STAPHYLOCOCCAL PULMONARY INFECTION

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IN recent years it has been widely recognised that staphylococcal bronchopneumonia is a lethal disease in hospital patients (e.g., Brownrigg 1955, Gresham and Gleeson-White 1957). But the fact that the human lung may be a major reservoir and source of hospital cross-infection has not had enough attention (Shooter et al. 1957). Until now, efforts to control hospital infection have dealt mainly with fomites, nasal carriers, and individual patients with surface infections (e.g., Williams et al. 1959, Gillespie et al. 1959). A full review is given by Williams et al. (1960).

At the Law Hospital, staphylococcal lung infection has been commonly found in patients dying from any cause. Though only a minority died solely because of this infection, it could not always be dismissed, in the other cases, as a terminal event. A typical tragedy was that of the 45-year-old collier submitted to an elective partial gastrectomy for peptic ulcer, who died two or three weeks after operation. For the last week of his life he was known to have a progressive lung infection which finally killed him. At necropsy the operation site was perfectly healed, but the lungs showed multiple abscesses. The organism found in the lungs was of a resistant hospital type of *Staphylococcus aureus*.

An inquiry covering 150 consecutive necropsies in this hospital was made between September, 1959, and August, 1960. During this period there were 575 deaths in the hospital and roughly 25% came to necropsy.

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The hospital is divided into four units, each widely separated from the other—surgical (174 adult beds), orthopædic (120 beds), general medical (170 beds), and geriatric (84 beds). In this paper "surgical deaths" include deaths in the orthopædic unit and "medical deaths" include geriatric.

Methods

The average time from death to necropsy was just less than twenty-four hours, and in only 3 cases was it more than forty-eight.

Cultures

Cultures were taken routinely from each lung and the spleen. The posterior surface of the lungs was exposed by drawing forward the tissues of the neck and thorax. The surface of the middle of each lower lobe was seared and a small incision made with a sterile scalpel to permit easy access of the swab. The spleen was similarly incised and swabbed. Further cultures from other sites were taken if indicated.

Each swab was used to inoculate plates of blood-agar and chocolate-agar, and was finally placed in meat broth containing 10% sodium chloride. The media were then incubated at 37°C overnight. If no obvious growth of staphylococci occurred on primary culture, a subculture was made on blood-agar from the salt broth. Any growth of coagulase-positive *Staph. aureus* obtained in this way was described as scanty. Henceforth the terms staphylococcus and *Staph. aureus* refer to coagulase-producing organisms.

The sensitivity pattern of each strain isolated was determined against penicillin (0·5 I.U.), tetracycline (10 μg.), streptomycin (20 μg.), chloramphenicol (40 μg.), and erythromycin (1 μg.). Evans' 'Sentests' were used for this purpose. Finally the strains of *Staph. aureus* isolated from each source were phage-typed by one of us. The technique employed was that described by Anderson and Williams (1956).

TABLE I—INCIDENCE OF STAPHYLOCOCCI ISOLATED FROM LUNGS AND OF LUNG SEPSIS AT NECROPSY

Number of days after admission (1)	Number of deaths (2)	Number yielding staph. (3)	% yielding staph. (4)	Number yielding hospital staph. (5)	Number of (3) with lung sepsis (6)
0	18	3	17	0	0
1	24	7	29	2	1
2–3	11	5	45	1	4
4–7	12	5	42	2	4
8–15	33	24	73	17	13
16–31	23	17	74	17	11
32–63	17	13	76	11	8
64+	12	10	83	8	6
Total ..	150	84	55	58	47

TABLE II—INCIDENCE OF STAPHYLOCOCCI IN SEPTIC AND NON-SEPTIC LUNGS AT NECROPSY

Number of days after admission	Total		Septic lungs				Non-septic lungs		
	Number of deaths	% with lung sepsis	Number of deaths	Number with staph.	Number with hospital staph.	Number of (4) admitted with acute lung infection	Number of deaths	Number with staph.	Number with hospital staph.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
0	18	11	2	0	0	2	16	3	0
1	24	17	4	1	1	4	20	6	1
2–3	11	64	7	4	0	7	4	1	1
4–7	12	42	5	4	2	3	7	1	0
8–15	33	48	16	13	9	6	17	11	7
16–31	23	48	11	11	11	3	12	6	6
32–63	17	53	9	8	8	0	8	5	4
64+	12	50	6	6	5	1	6	4	3
Total	150	40	60	47	36	26	90	37	22

TABLE III—INCIDENCE OF PHAGE-TYPES IN HOSPITAL AND NON-HOSPITAL STRAINS OF STAPHYLOCOCCI

Group	Hospital staph.	Non-hospital staph.	Uncertain
I { Type 80	16	0	0
I { Other	7	3	2
II	0	3	0
III	20	10	1
Mixed groups	13	4	1
Not typeable	2	2	0
Total	58	22	4

The determination of hospital strains was based primarily on the antibiotic sensitivity pattern and the phage-type; in some cases aided by the case-history. Strains resistant to penicillin, streptomycin, and/or the tetracyclines were designated hospital strains.

Lung Sepsis

To avoid bias, the evidence of lung sepsis was examined by one of us without knowledge of the bacteriological findings. Gross lesions such as bronchopneumonia and lung abscess presented little difficulty, but bronchiolitis without obvious consolidation required histological examination. If a purulent exudate was then found in the alveoli the lung was regarded as septic. Lesions were encountered, notably hæmorrhage and infarction, in which the role of sepsis was doubtful; these were excluded unless there was concomitant bronchopneumonia.

Results

Incidence of Staphylococcal Invasion of Lungs

In table I the frequency with which staphylococci were isolated from the lungs is related to the interval between admission and death. The figure at zero time indicates death on the day of admission. The overall incidence was 84 out of 150 (55%), of which 58 (69%) were hospital strains. If we exclude deaths within a week of admission, the incidence was 64 out of 85 (75%), of which 53 (82%) were hospital strains. The numbers of hospital strains given here exclude 4 which could not be categorised clearly as of hospital or non-hospital origin (table III). It is worthy of note that 16 of the hospital strains isolated were of phage-type 80. This strain has been present in the hospital at least since May 1958 (Mitchell et al. 1959).

Incidence of Lung Sepsis

Lung sepsis was associated with 40% of all deaths and with 50% of deaths eight or more days after admission (table II). Though there was no progressive increase in the proportion of cases of lung sepsis with increasing stay in hospital, there was a progressive increase in the frequency with which staphylococci were isolated from lungs with obvious sepsis. Staphylococci were isolated from septic lungs more often than from non-septic ones. Of the 18 patients who died within a week of admission with lung sepsis, 16 were admitted with clinical signs of acute respiratory infection, and 3 of these yielded hospital staphylococci. On the other hand, of the 42 who died eight or more days after admission, only 10 were admitted with acute respiratory infection, 7 of these yielding hospital strains of *Staph. aureus*. Of the 5 hospital strains isolated under eight days, 2 were obtained from patients who had recentiy been discharged from hospital and readmitted.

These results suggest that lung sepsis in patients dying more than a week after admission is predominantly a consequence of, or at least associated with, staphylococcal infection by an organism acquired in hospital.

Factors Affecting Incidence of Hospital Lung Sepsis

The only factor found to affect the incidence of sepsis was the presence of pre-existing chronic lung disease—namely, chronic bronchitis and emphysema, industrial dust diseases, bronchogenic carcinoma, and tuberculosis. Septic lungs from which staphylococci were isolated were found in 28 of 69 (41%) cases with pre-existing chronic lung disease but in only 19 of 81 (24%) of other cases (table IV). The principal local industries are coalmining and the heavy steel industry, and 48 men who came to necropsy had been employed in dusty occupations (table V). Of these, 20 had frankly septic lungs from which staphylococci were isolated; in 8 more the lungs showed sepsis but no staphylococci were isolated.

The incidence of infection was not influenced by the age or sex of the patients, nor by the units to which they had been admitted, nor was it dependent on the time of year. In 13 cases there were lung infarcts, but there was no evidence that these were important as sites of lung sepsis.

TABLE V—INCIDENCE OF LUNG SEPSIS IN PATIENTS WHO WERE WORKERS IN DUSTY TRADES

Number of days after admission (1)	Number of deaths (2)	Number with staph. (3)	Number with hospital staph. (4)	Number with lung sepsis (5)	Number of (5) with staph. (6)
0–1	13	1	0	4	0
2–7	6	3	0	5	3
8–15	16	10	7	9	7
16+	13	12	12	10	10
Total ..	48	26	19	28	20

The profuseness of growth of the staphylococci could not be correlated with the extent of lung sepsis. Of 23 strains isolated only from salt broth, 7 were from patients with lung sepsis. The time between death and necropsy did not seem to innuence the probability of isolating staphylococci in the time range within which most of the necropsies were carried out.

Lung Sepsis and Wound Infection

Staphylococcal Septicæmia

From routine spleen cultures staphylococci were isolated in 20 cases. There was a positive lung culture of the same strain in each of these cases, and 17 had frank

TABLE IV—INCIDENCE OF STAPHYLOCOCCI AND OF SEPSIS IN CHRONIC LUNG DISEASE AND IN PREVIOUSLY HEALTHY LUNGS

Number of days after admission (1)	Chronic lung disease: Number (2)	Number with staph. (3)	Number with hospital staph. (4)	Number with lung sepsis (5)	Number of (5) with staph. (6)	Healthy lung: Number (7)	Number with staph. (8)	Number with hospital staph. (9)	Number with lung sepsis (10)	Number of (10) with staph. (11)
0–1	17	0	0	5	0	25	10	2	1	1
2–7	10	6	0	8	5	13	4	3	4	3
8–15	17	11	8	10	7	16	13	9	6	6
16+	25	22	20	17	16	27	18	16	9	9
Total ..	69	39	28	40	28	81	45	30	20	19

lung sepsis. Of the other 3, 1 died on the day of admission with bilateral suppurative pyelonephritis (from which no staphylococci were isolated), 1 had a stone in the common bile-duct, and 1 had amyloid disease associated with rheumatoid arthritis and pyelonephritis. The failure to develop lung sepsis in the last case was unexpected, since the patient had been in hospital for eighty days and had been given cortisone.

Septicæmia derived from lung sepsis is therefore common, 17 out of 60 (28%) cases, or 13 out of 42 (31%) cases dying after the seventh day. In no case was a positive spleen culture obtained from a subject who did not also show a positive lung culture. Many of these patients died weeks after lung sepsis was clinically obvious. This confirms the findings of Smith et al. (1960) that the lungs are a common primary focus for septicæmia.

Metastatic Abscess from Lung

The possibility of metastatic abscess first came to our attention four years ago when we were examining a series of unexpected postoperative deaths after elective surgery for peptic ulcer. These patients, many of whom were colliers, died about a week after operation performed after several weeks' preoperative treatment in hospital. The findings at necropsy were fairly constant. The stomach remnant and intestine round the operation site were congested and friable—indeed sometimes gangrenous—with tearing of the sutures and a poorly localised upper-abdominal peritonitis. From some of these operation sites *Staph. aureus* was isolated, and the lungs were usually septic. At first we thought that events leading to death had begun with a burst suture line. In retrospect we believe that in some of these cases the sequence of events was the other way round—staphylococcal penetration of the lung before operation, postoperative pulmonary collapse with sepsis, septicæmia, and finally deep wound infection.

It is of interest that there were few similar cases in this series. We isolated *Staph. aureus* from 5 cases of post-operative peritonitis. In each the organisms isolated from the abdominal cavity were of the same phage-type as those present in the lung, and in 2 cases in the spleen as well. All had been in hospital for over eight days, 4 of them showed lung sepsis, and the 5th had lung collapse.

It may be argued that the abdominal infection was not blood-borne even if derived from the lung. But there is no other explanation than septicæmia for a staphylococcal meningitis in a patient in this series who died eight days after admission for cerebral infarction. It is significant that here the same organism was isolated from the lungs and brain despite the absence of frank pulmonary sepsis.

We conclude, therefore, that septicæmia may be common in staphylococcal lung infections, with or without sepsis. We suggest, moreover, that septicæmic dissemination may be a cause of deep wound infections.

The Lung as Source of Superficial Wound Infection

All staphylococci isolated from infections found in the four units of the hospital during the period of the inquiry were phage-typed. These were mostly skin and wound infections (table VI). There is a rough correlation between the frequency of the different types found in these infections and in the lungs at necropsy in patients from the same wards.

TABLE VI—INCIDENCE OF PHAGE-TYPES OF STAPHYLOCOCCI ISOLATED FROM PATIENTS IN WARDS AND FROM SUBJECTS AT NECROPSY

	Phage-type (1)	Hospital infection			Non-hospital infection		
		Skin (2)	Sputum (3)	Post-mortem lung (4)	Skin (5)	Sputum (6)	Post-mortem lung (7)
Surgical	Group I { 80	38	1	7	6	0	0
	Group I { Other	13	0	1	5	0	2
	Group II	5	0	1	9	0	2
	Group III	7	2	7	8	0	5
	Mixed groups and untypeable strains	21	1	6	14	0	1
	Total	84	4	22	42	0	10
Medical	Group I { 80	15	5	9	4	0	0
	Group I { Other	3	3	6	7	1	3
	Group II	2	0	0	6	1	1
	Group III	6	12	13	4	5	6
	Mixed groups and untypeable strains	16	1	7	8	5	4
	Total	42	21	35	29	12	14

Gosling et al. (1959) reported on the relation between (*a*) staphylococcal skin infection and (*b*) staphylococci found in the lungs of patients with staphylococcal pneumonia following influenza. The same relation is evident when patients with skin infections are in contact with patients with chronic lung disease in the same ward. Probably, too, the same process occurs in reverse—i.e., staphylococci are disseminated from septic lungs, and cause, directly or indirectly, further wound, skin and lung infections in other patients. *Staph. aureus* was isolated from the sputa of 37 patients who all had clinical signs of lung disease. Maccabe (1959) noted the frequency of hospital cross-infection to the lungs. It is also of note that *Staph. aureus* of phage-type 80 was isolated on 10 occasions from patients on admission. In only 1 case (a breast abscess) had the patient been recently in hospital. Hassall and Rountree (1959) noted the increase of staphylococcal septicæmia due to this strain in patients infected outside hospital.

Postoperative Deaths

Of the 150 cases 25 had undergone some form of major surgery. Of these, 22 had died eight or more days after admission. The incidence of lung staphylococci and sepsis was the same as for all patients dying in the surgical units; 17 had positive lung cultures and 11 evidence of lung sepsis.

What is more important, in 5 of the deaths the hospital-induced lung sepsis could be regarded as the primary cause of death. This incidence of fatal postoperative lung infection is lower than we had expected from past experience.

Staphylococcal Lung Sepsis as Cause of Death

Of the 47 cases dying with overt lung sepsis from which staphylococci were isolated, we estimated that in 9 cases it was the primary factor—i.e., that in the absence of lung sepsis the patient would probably have survived. In each instance the patient had been in hospital for more than seven days, and all yielded hospital strains of *Staph. aureus*.

We give two illustrative cases:

1. Collier, aged 61. Admitted with perforated vermiform appendix. He was successfully operated upon. Slow recovery followed, but about the twentieth day the patient became febrile and signs of pneumonia were found. He died on the twenty-fourth day. Necropsy revealed a small retrocæcal abscess the size of a pea and anthracosilicosis of the lungs with pulmonary abscesses. *Staph. aureus* of phage-type 80 was isolated from both lungs, the spleen, the retrocæcal abscess, and the abdominal wound.

2. Housewife, aged 69. Admitted for control of diabetes mellitus. This was effected at the end of three weeks. A week later she developed pneumonia. *Staph. aureus* of phage-type 6/47/53/54/75/77 was isolated from the sputum. Initially the lung infection appeared to respond to treatment, but the patient's condition deteriorated, and she died on the sixtieth day. At necropsy, multiple lung abscesses which yielded *Staph. aureus* of phage-type 6W/47/75/77 were found.

Conclusions

From the experience of this hospital we conclude that:

1. A major reservoir of hospital staphylococci, and a possible source of skin and wound infection, is the lungs of the patients. By reservoir we mean a discharging open pyogenic focus.

2. Patients who are in hospital for more than seven days tend to become infected with hospital strains of *Staph. aureus* in their lungs.

3. Patients admitted with chronic lung disease are more liable to develop lung sepsis associated with hospital staphylococci, than other patients.

4. Staphylococcal bronchopneumonia, or lung abscess, is a common accessory and occasionally a primary factor in death after abdominal operation, or indeed after admission to hospital at all.

5. The lung is a common primary site of staphylococcal septicæmia, and this may be a source of deep wound infection.

During the past five years bacteriological surveys of fomites, personnel, and equipment, as sources of staphylococcal infection, have been carried out in this hospital. Although appropriate counter-measures have been applied, such infection has persisted, as may be seen from the continued presence of *Staph. aureus* type 80.

It is questionable whether patients with chronic chest disease should be admitted to hospital unless this is essential. Admission often results in their deaths, even if the chest disability is not severe. What is more important, a possibly fatal infection may be transmitted to other patients. Some effort must be made to isolate patients with chronic and postoperative lung infections (Williams et al. 1960).

Imperative surgery should be undertaken as soon as practicable after admission. Delay of a week greatly increases the hazards of staphylococcal infection, particularly of the lungs and particularly in patients with chronic bronchitis.

Elective operations, particularly in patients over 65, should also be performed as soon as possible after admission, and only if the consequences of not operating are more likely to prove fatal. Protracted convalescence in hospital should be avoided.

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REFERENCES

Anderson, E. S., Williams, R. E. O. (1956) *J. clin. Path.* **9**, 94.
Brownrigg, G. M. (1955) *Canad. med. Ass. J.* **73**, 787.
Gillespie, W. A., Alder, V. G., Ayliffe, G. A. J., Bradbeer, J. W., Wypkema, W. (1959) *Lancet*, ii, 781.
Goslings, W. R. O., Mulder, J., Djajadiningrat, J., Masurel, N. (1959) *ibid.* p. 428.
Gresham, G. A., Gleeson-White, M. H. (1957) *ibid.* i, 651.
Hassall, J. E., Rountree, P. M. (1959) *ibid.* i, 213.
Maccabe, A. F. (1959) *Scot. med. J.* **4**, 75.
Mitchell, A. A. B., Timbury, M. C., Pettigrew, J. B., Hutchison, J. G. P. (1959) *Lancet*, ii, 503.
Shooter, R. A., Griffiths, J. D., Cook, J., Williams, R. E. O. (1957) *Brit. med. J.* i, 433.
Smith, I. M., Vickers, A. B. (1960) *Lancet*, i, 1318.
Williams, R. E. O., Blowers, R., Garrod, L. P., Shooter, R. A. (1960) Hospital Infection: causes and prevention; p. 24. London.
— Jevons, M. P., Shooter, R. A., Hunter, C. J. W., Girling, J. A., Griffiths, J. D., Taylor, G. W. (1959) *Brit. med. J.* ii, 658.

THE DUMPING SYNDROME

An Investigation and a Cause

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SOME of the clinical features of natural dumping attacks, referred to previously (Cox and Allan 1960), suggest that vascular dilatation is the cause. We have therefore measured the blood-pressure, pulse-rate, and hæmatocrit, and studied the blood-volume changes by means of plethysmograph recordings, during dumping attacks which were reproduced by means of normal food.

The Investigation

METHODS

The hæmatocrit was estimated on venous blood without the use of a tourniquet. The blood-pressures were measured on the opposite arm.

In the plethysmograph which we used the volume changes are converted to electrical impulses by means of a transducer: they are then amplified and recorded on a 'Transwrite' electrocardiograph. The recordings were taken from a toe, to which the rim of the glass cup was sealed with 'Plasticine'; the temperature of the room was 23°C. An increase in the size of the deflection in the graph means an increase in pulse volume, which indicates vasodilatation in the peripheral vessels. The converse is also true. We shall therefore refer to changes in size of the deflection in terms of peripheral vasodilatation or vasoconstriction. A change in the deflection in any series of recordings should be compared with the control in that particular series.

HÆMATOCRIT, BLOOD-PRESSURE, AND PULSE-RATE

The patients studied were three males and three females, whose average age was 48, the youngest being 29 and the oldest 70. Three had undergone routine partial gastrectomy (one Polya and two Schoemaker), and three had had 50% partial gastrectomies with vagotomy. All had dumping symptoms. The time-interval between operation and our studies varied from 1 to 6 years, the average being 4 years.

BLOOD-PRESSURE (mm. Hg) AND PULSE-RATE (PER MIN.) RECORDINGS DURING DUMPING ATTACKS WITH THE PATIENT RECUMBENT

Case no.	Preliminary		Onset of dumping		At 10 min.		At 20 min.		Final	
	B.P.	P.	B.P.	P.	B.P.	P.	B.P.	P.	B.P.	P.
1	110/70	60	120/70	64	110/70	64	110/65	72	110/65	68
2	115/80	96	120/85	108	120/85	108	125/90	112	125/90	112
3	130/80	78	130/80	80	135/85	82	130/80	82	125/80	80
4	120/90	76	125/95	96	135/95	88	125/90	68	125/90	68
5	120/70	72	110/70	84	110/65	80	110/60	80	110/60	60
6	155/80	50	170/90	50	170/90	56	160/85	56	155/85	50
7	155/95	88	160/100	100	160/100	100	160/100	100	160/100	92

The food responsible for reproducing the attacks was 8 oz. (225 ml.) of milk containing a beaten-up egg, with or without 8 g. (2 teaspoonfuls) of sugar, at a temperature of 135°F.

During seven dumping attacks with the patients recumbent, there was no significant change in the hæmatocrit values, but the blood-pressure and pulse-rate rose slightly in most cases (see table). We therefore took blood-pressure and pulse recordings with the patients erect during these attacks:

Case 1.—Male, aged 63. Vagotomy and pyloroplasty in 1951. Dumping attack brought on in 4 minutes by 8 oz. of milk and egg at 128°F, and one bar of milk chocolate. The blood-pressure fell from 155/100 to 130/80 mm. Hg, and did not rise

with slow walking. The pulse-rate rose from 80 to 100 per minute.

Case 2.—Male, aged 70. Routine partial gastrectomy (Polya) in 1955. Dumping attack brought on by 8 oz. of milk and egg at 130°F. The blood-pressure fell from 130/85 to 100/? immediately after he had finished the drink. The pulse-rate rose from 80 to 112 per minute without walking.

Case 3.—Male, aged 45. Vagotomy and hemigastrectomy (Polya) in 1960. Dumping attack brought on by 8 oz. of milk and egg at 128°F. The blood-pressure fell from 155/100 to 120/85, and the pulse-rate rose from 68 to 96 per minute in 7 minutes. Moderately severe symptoms of dumping came on in 5 minutes without any walking.

Case 4.—Female, aged 60. Routine partial gastrectomy (Polya) in 1954. Dumping attack brought on in 3 minutes by 8 oz. of milk and egg at 128°F. The blood-pressure fell from 160/95 to 140/65 with slow walking, and the pulse-rate rose from 90 to 118 per minute.

Thus, when the readings were taken in the standing position both the systolic and diastolic pressure fell in every case—the systolic by 20–35 and the diastolic by 15–30 mm. Hg. The pulse-rate rose by 20–32 per minute. These attacks of dumping were therefore associated with hypotension. The cause of the slight rise in blood-pressure when recumbent during dumping, which was not at first obvious, is now thought to be an overcompensation for the preceding fall.

PLETHYSMOGRAPH RECORDINGS

Control Recordings

A series of plethysmograph recordings was made after 8 oz. of milk-and-egg mixture, with 8 g. of sugar, at 128°F.

Before gastric surgery.—In seven patients, shown radiologically to have a normal gastric emptying-time, there was no change in the readings during 30 minutes.

After cholecystectomy.—In five patients, during the 3rd week after cholecystectomy, there was no change in the recordings during 30 minutes (see figure [*a*]).

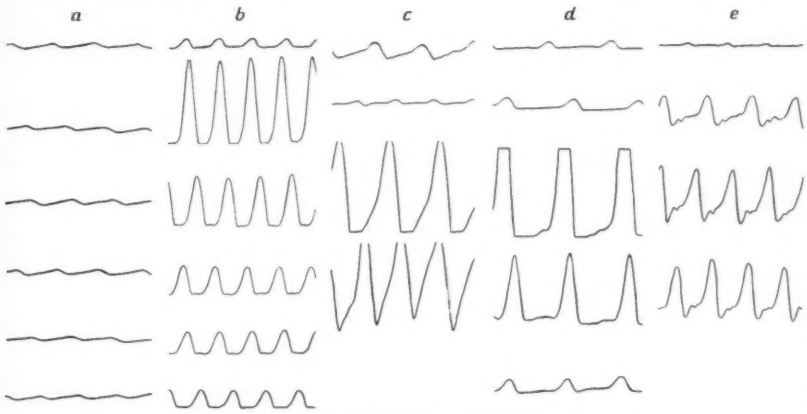
No peripheral vasodilatation was shown by means of the plethysmograph before gastric surgery or after a "control" operation such as cholecystectomy. This suggests that it is the nature of the gastric operation which determines the subsequent peripheral vascular changes.

After Routine Gastric Surgery

Recordings were taken after 8 oz. of milk-and-egg mixture at 128°F, during the 3rd week after gastric surgery, from twenty-seven patients in the recumbent position and from ten of these when standing as well. In seventeen cases the mixture was sweetened with 8 g. of sugar, and in ten it was unsweetened. The operations were routine 75% partial gastrectomy, vagotomy with posterior gastroenterostomy, vagotomy with 50% partial gastrectomy, and in one case vagotomy with pyloroplasty. No patient in this group experienced any symptoms of dumping.

In the *recumbent position*, all twenty-seven recordings showed considerable peripheral vasodilatation (see figure [*b*]). The first and the last readings were taken 6 and 30 minutes after the patients started to drink. In fourteen the vasodilatation reached its maximum at the 6-minute reading, and in thirteen at the 12–18-minute reading. At the 30-minute reading the recording had returned to normal in the majority of cases. To detect the earliest onset of vasodilatation, readings were taken in five cases immediately after the patient started to drink. Though less accurate than those taken after 6 minutes, these showed that vasodilatation can begin within 1 minute.

In the *erect position*, the recordings showed complete absence of vasoconstriction in seven cases, slight vasoconstriction in two and further vasodilatation in one (see figure [*c*]). Previous recordings from these ten patients, in the recumbent and erect positions, with the stomach empty (three hours after their last meal) had shown, as expected, normal vasoconstriction on standing. We have no evidence to offer as to the state of the blood-vessels in the splanchnic area or in the muscles, but dilatation in the splanchnic area is to be expected.



Plethysmograph recordings from the second toe.

The first reading in each case is a control taken in the recumbent position.

(*a*) Female, aged 35; 3rd week after cholecystectomy. Recordings taken in the recumbent position at 6-minute intervals after 8 oz. of sweetened milk and egg at 128°F. These are normal readings similar to those before gastric operations.

(*b*) Female, aged 61; 3rd week after vagotomy and posterior gastroenterostomy. The readings, taken recumbent at 6-minute intervals after 8 oz. of sweetened milk and egg at 128°F, show typical vasodilatation.

(*c*) Male, aged 21; 3rd week after vagotomy and 50% partial gastrectomy (Polya). The second reading shows vasoconstriction on standing. 8 oz. of sweetened milk and egg at 128°F was then given; the third reading 6 minutes later shows vasodilatation when recumbent, and the fourth reading shows failure of vasoconstriction on standing.

(*d*) Male, aged 33; 3rd week after partial gastrectomy (Polya). The second reading shows the maximum effect of 8 oz. of tea without milk or sugar at 128°F. The third reading was taken 10 minutes after 8 oz. of sweetened milk and egg at 128°F, and the other readings at 10-minute intervals.

(*e*) Normal female, aged 21. The readings, taken over a period of 15 minutes, show reflex vasodilatation produced by external heat, to the point of sweating.

Effect of Temperature and Composition of the Food

The effects of 8 oz. of milk and egg at 128°F and at 98°F, and of tea without sugar or milk at 128°F, were compared.

Before gastric surgery, in seven patients, neither fluid at 128°F produced a change in the recording over 30 minutes.

During the 3rd week *after gastric surgery*, 30-minute recordings in thirteen patients after 8 oz. of tea at 128°F showed no vasodilatation in five cases, and slight vasodilatation in eight. Recordings in seven patients after the milk-and-egg mixture at 98°F showed slight vasodilatation in two cases, and moderate vasodilatation in five; the same seven patients, after milk and egg at 128°F, all showed considerable vasodilatation (see figure [*d*]).

In Patients who had Natural Dumping Attacks

There were three patients in this group. Dumping attacks were induced by 8 oz. of milk-and-egg mixture at 128°F, and in one case this was sweetened with 8 g. of sugar. When the dumping attack came on, recordings were taken with the patient lying and standing.

In each case the plethysmograph showed considerable vasodilatation with the patient lying, and no vasoconstriction with the patient standing.

To show how significant these plethysmograph recordings are, we compared them with a known standard—namely, the maximum reflex peripheral vasodilatation produced by external heat:

One arm up to the elbow, and one leg up to the knee, of a normal woman aged 21, were placed in water at 115°F, and an electric blanket was placed over her abdomen and thighs. Three recordings were taken over 15 minutes, during which time she had become hot and was sweating (see figure [*e*]).

These recordings show that the degree of peripheral vasodilatation produced by the ingestion of the milk-and-egg mixture at 128°F after gastric surgery is comparable to the maximum reflex peripheral vasodilatation produced by external heat.

Summary of the Plethysmograph Evidence

We found that before gastric surgery—i.e., in the presence of a normal gastric-emptying mechanism—neither the hot fatty mixture we used, nor hot tea without milk or sugar, produced peripheral vasodilatation during 30 minutes. After gastric surgery, when the normal gastric-emptying mechanism has been removed or bypassed, the milk-and-egg-mixture at 128°F, sweetened or unsweetened, produced considerable peripheral vasodilatation. The same mixture at 98°F produced definite peripheral vasodilatation, but not so much as at 128°F. An inappreciable degree of peripheral vasodilatation followed tea without milk or sugar at 128°F. On standing during the period of vasodilatation the vasoconstriction mechanism is ineffective, and so the vasodilatation persists.

Comparing these findings with those during the dumping attack, we find no difference in the degree of peripheral vasodilatation or vasoconstriction on standing between those with dumping symptoms and those without.

Discussion

Partial gastrectomy and other similar operations bring about a radical change in the patient's reaction to fatty foods. After gastric surgery these foods produce an unstable vascular state, with peripheral vasodilatation and failure of peripheral vasoconstriction on standing. The tone of the vessels of the skin, and the ability to vasoconstrict on standing, are two important mechanisms which help to maintain peripheral resistance. After partial gastrectomy, both are disrupted when fatty foods are taken.

Similar instability of the vascular state is produced in normal people on exposure to external heat, for the same reasons. We may quote Samson Wright (1952):

"Normally, on passing from the horizontal to the erect position blood vessels in the legs are reflexly constricted . . . but during heat exposure vascular tone is dominated by temperature requirements, and the normal postural adjustments do not occur. Thus, in hot environments, the subject . . . soon *faints* if he is passively tilted from the horizontal towards the erect position and kept there for some time . . ."

This brings to mind our previous experience in which an attack of dumping, relieved when the patient lay horizontal on the X-ray table, was brought on again by tilting the table from the horizontal towards the vertical.

The symptoms of the dumping attack are also the symptoms of hypotension—weakness, light-headedness, palpitation, and visual disturbances—with the addition of alimentary symptoms. This strongly suggests that the attacks are associated with hypotension, and our recording a fall in blood-pressure and a rise in pulse-rate during dumping when the patients were standing confirms this.

In view of our findings, it is reasonable to suggest that the following sequence of events is responsible for the dumping attack. The removal or bypassing of the normal gastric-emptying mechanism by surgery allows fatty and/or sweet foods to pass straight into the upper intestine. Hyperperistalsis carries these foods rapidly down the intestine, thus exposing a large internal surface to their full effects—undigested, and at a temperature not much below the original. This rapidly produces striking peripheral vasodilatation. In the recumbent position the patient can compensate adequately for this vasodilatation, the blood-pressure does not fall, and there are no symptoms. But when the patient stands an additional strain is imposed on the compensatory mechanisms by the failure of reflex vasoconstriction. In those unable to compensate, the blood-pressure falls, and symptoms of hypotension develop.

The above hypothesis explains how posture and hotter food can determine the development of the dumping attack, and why dumping can develop very rapidly—within 2 minutes of taking hot fatty foods. An increase in surrounding temperature can by itself cause vasodilatation and therefore increase the tendency to dump. Exercise adds a further strain to a circulation already embarrassed by peripheral dilatation and failure of vasoconstriction. Intestinal stasis, which has previously been described (Cox and Allan 1960), is explicable on the basis of a sympathetic adrenal response to the fall in blood-pressure. The stasis is thus part of the response mechanism, and it plays no part in causing the dumping attack.

Conclusions

The problem of the dumping attack is one of an unstable vascular state. The inability to react by vasoconstriction on standing, added to considerable peripheral vasodilatation, deprive the patient of an important defence mechanism against a fall in blood-pressure. The attack itself is a form of postural hypotension which is usually associated in variable degree with alimentary symptoms.

It is a pleasure to thank the patients for their willing cooperation; Mr. Sidney Rose for the use of his modified plethysmograph; the Regional Board for financial assistance; and our department of medical illustrations.

REFERENCES

Cox, H. T., Allan, W. R. (1960) *Lancet*, ii, 1261.
Wright, S. (1952) Applied Physiology; p. 477. London.

PITUITARY AND ADRENAL FUNCTION DURING ADMINISTRATION OF SMALL DOSES OF CORTICOSTEROIDS

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CARDIFF ROYAL INFIRMARY

THE present investigation stems from the observation that daily doses of prednisolone as small as 5 mg. or less may be therapeutically effective in rheumatoid arthritis and in idiopathic thrombocytopenic purpura. This dose is equivalent to some 25 mg. cortisone acetate which is of the same order as the daily output of cortisol by the adrenal (Peterson and Wyngaarden 1956).

If it is assumed that such small doses of exogenous steroid are insufficient to suppress the pituitary (and

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hence the adrenal), then their therapeutic effect could be regarded as being produced by the sum of exogenous and endogenous steroid. We therefore looked for this additive effect by measuring the changes in urinary 17-hydroxy-cortisteroid (17-O.H.C.S.) metabolites before and during administration of small doses of cortisone. The response of the adrenal and pituitary to stimulation was also studied in patients receiving various doses of corticosteroid.

Material and Methods

Male and female patients aged 21–70 years were studied in one of two ways. In one study in six patients who had never previously taken corticosteroids, the daily urinary output of corticosteroid metabolites was measured before and during administration of cortisone. Cortisone acetate was given orally in equal doses at 10 A.M. and 6 P.M., the dose being increased at two- or three-day intervals. There were two groups of patients in the second study: (1) a control group of five patients who were convalescing from various non-endocrine diseases and who had never taken corticosteroids, and (2) a group of fourteen patients, thirteen with rheumatoid arthritis and one with idiopathic thrombocytopenic purpura, who were all receiving corticosteroids in doses equivalent to 25–100 mg. of cortisone a day.

The corticosteroids given were prednisolone, prednisone, methyl prednisolone, triamcinolone, and dexamethasone. For simplicity all doses will subsequently be referred to as "cortisone equivalents", taking 25 mg. cortisone = 5 mg. prednisolone = 5 mg. prednisone = 4 mg. methylprednisolone = 4 mg. triamcinolone = 0·75 mg. dexamethasone. The total duration of corticosteroid therapy in these patients ranged from 2 to 54 months (mean 26 months).

At the time of investigation the disease was adequately controlled in all of the patients by a dose of corticosteroid which had not been varied during the previous 2–48 months (mean of 15 months). In this (second) study, adrenal and pituitary function was tested in the control and corticosteroid-treated groups of patients by infusion of corticotrophin (A.C.T.H.) and by injection of pyrogen. Bacterial pyrogen stimulates pituitary secretion of corticotrophin (Conn et al. 1954, Wexler et al. 1957 and 1958) and has been used as a test of pituitary function (Ferriman and Page 1960). The response to corticotrophin and pyrogen was measured by the changes in the plasma-cortisol concentration. The patients were put to bed and the tests were started shortly before mid-day, the treated patients taking their usual dose of corticosteroid.

25 I.U. of corticotrophin (Organon) in 1 litre 0·9% sodium chloride was infused over 4 hours, and blood was drawn immediately before and at intervals during the infusion. This dose of corticotrophin gives a maximal adrenal response in normal subjects (Eik-Nes et al. 1954, Christy et al. 1955).

Bacterial pyrogen (Organon) was injected intravenously in doses of 0·005 μg. per kg. body-weight. Blood was taken immediately before and at intervals after the injection. The temperature of all the patients had risen to 99°F within 1 to 2 hours of the injection and had returned to normal after 5 to $10^1/_2$ hours, in most of the patients the pyrexia being preceded by a rigor. The maximum temperatures ranged from 100°F to 103°F and were reached from $1^1/_2$ hours to $3^1/_2$ hours after the injection. All blood samples were drawn into heparin; the plasma was separated and stored frozen until analysed.

Urinary glucuronide-conjugated 17-O.H.C.S. were measured with the Porter-Silber reagent (Silber and Porter 1954), after incubating the urine with Limpet β-glucuronidase (1000 Fishman units per ml.) for 48 hours at 37°C at pH 4·5 with acetate buffer.

Plasma-cortisol was measured by the method of Peterson et al. (1957) with slight modifications (Hatfield and Shuster 1959). This measures plasma free 17-O.H.C.S. with the Porter-Silber reagent. Using this method we find that the plasma-cortisol concentration in normal subjects falls within the range of 4–26μg. per. 100 ml. plasma. Triamcinolone is not detected in the blood by this method even with relatively large doses (Hatfield and Shuster 1959). Demaxethasone was used in a dosage of 1·5 mg. a day, which is too small to have a measurable effect on the plasma free 17-O.H.C.S. In three patients, however, prednisolone was given in doses of 15–20 mg.—amounts that would themselves have increased the plasma-free 17-O.H.C.S. concentration. With the exception, therefore, of these three patients the plasma-free 17-O.H.C.S. concentration can be taken to represent endogenous cortisol (as it does in normal subjects [Bush and Sandberg 1953]).

Results

Urinary 17-O.H.C.S. Metabolites with Oral Cortisone

The urinary excretion of 17-O.H.C.S. metabolites in six patients before and during administration of cortisone is shown in fig. 1. Despite the considerable individual variation, the excretion of cortisone metabolites increased in all patients with doses of cortisone acetate of 12·5–37·5 mg.

Response to Corticotrophin and Pyrogen

The increase in plasma-cortisol concentration after pyrogen did not appear to be related to the febrile response, which was similar in all the groups of patients studied.

Controls

The response to corticotrophin and pyrogen in the patients who were not taking corticosteroids is shown in fig. 2. The maximum increase in plasma-cortisol concentration occurred 2–4 hours after pyrogen, and with one exception was less than the increase after corticotrophin in the same patient. For each individual the maximum increase in plasma-cortisol concentration after pyrogen was expressed as a percentage of the maximum increase after corticotrophin. The average increase after pyrogen was found to be 75% of that after corticotrophin.

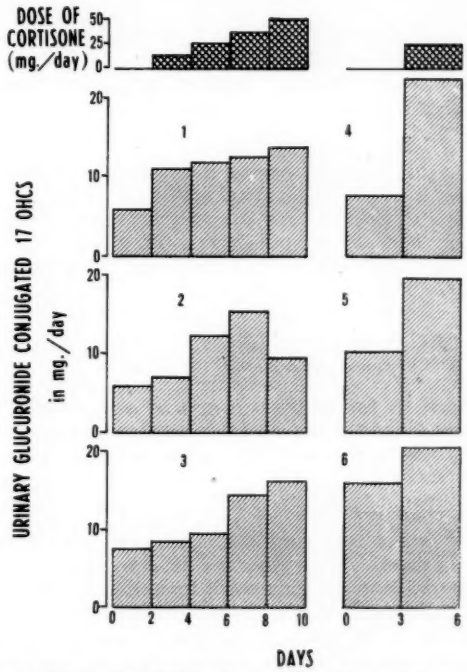

Fig. 1—Urinary 17-O.H.C.S. glucuronides before and during cortisone administration in six convalescent patients who had not previously taken cortisone.

Each block of 2 or 3 days is the mean steroid excretion over this period.

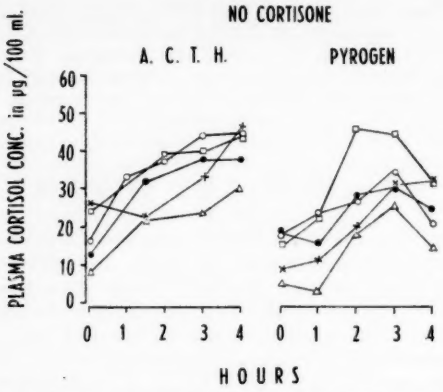

Fig. 2—Response to A.C.T.H. (corticotrophin) and pyrogen in the control group of five patients.
The results in individual patients are indicated by different symbols.

25 mg. "Cortisone Equivalents" (fig. 3)

The plasma-cortisol concentrations were normal before corticotrophin and with one exception before pyrogen. The responses to corticotrophin and pyrogen did not differ from those of the control patients (fig. 2), although the response to pyrogen was poor in one patient (fig. 3, x).

37·5 mg. "Cortisone Equivalents" (fig. 4)

In these patients the basal cortisol concentrations were less than in the controls but were within the range of normal. The response to corticotrophin and pyrogen was

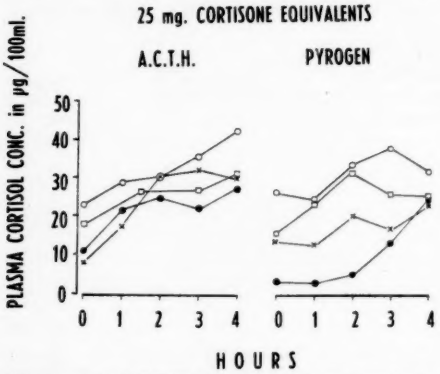

Fig. 3—Response to A.C.T.H. and pyrogen in four patients taking 25 mg. "cortisone equivalents".

less than in the controls; in two of the patients the response to pyrogen was slightly greater than the response to corticotrophin, but this difference may not be significant.

50 mg. "Cortisone Equivalents" (fig. 5)

The basal plasma-cortisol concentrations were normal in two patients. In the other two patients plasma-cortisol concentrations were subnormal, indicating adrenal suppression. There was a decreased response to corticotrophin in the group as a whole compared with the controls; only one patient showed a normal response to corticotrophin (fig. 5, open circles). By contrast the response to pyrogen was normal in three of the patients. In one there was no response to pyrogen despite some response to corticotrophin (fig. 5, closed circles).

75–100 mg. "Cortisone Equivalents" (fig. 6)

With doses of this order given as 15–20 mg. of prednisolone, the plasma-free 17-O.H.C.S. concentration was partly due to the exogenous steroid, an unknown fraction representing endogenous cortisol. There was some response to corticotrophin and pyrogen in one of the three patients (fig. 6, open circles).

Discussion

Inhibition of corticotrophin secretion with consequent adrenal suppression occurs during the administration of relatively large doses of corticosteroids (Ingle and Kendall 1937, Sayers 1950). If such inhibition occurred during administration of doses equivalent to, or less than, the daily secretion of cortisol by the adrenal, then the decreased adrenal secretion of cortisol would balance the increased intake of corticosteroid and the urinary

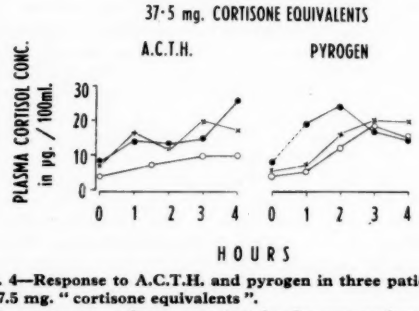

Fig. 4—Response to A.C.T.H. and pyrogen in three patients taking 37.5 mg. "cortisone equivalents".
A pre-pyrogen plasma was lost in the two patients shown as ●–● in figures 4 and 6. In both, the interrupted line joins a value assumed from the pre-corticotrophin cortisol concentrations.

17-O.H.C.S. output should be unchanged. The present finding of an increased urinary 17-O.H.C.S. excretion with doses of steroid equivalent to $12\frac{1}{2}$–$37\frac{1}{2}$ mg. of cortisone, which is equivalent to the normal range of cortisol output by the adrenal (Peterson and Wyngaarden 1956), demonstrates that no significant adrenal suppression had occurred, the increased urinary output of 17-O.H.C.S. being due to summation of endogenous and exogenous corticosteroid.

The investigation of pituitary and adrenal function in patients receiving various doses of corticosteroids supports this view since with doses equivalent to 25 mg. of cortisone the adrenal response to corticotrophin and the pituitary

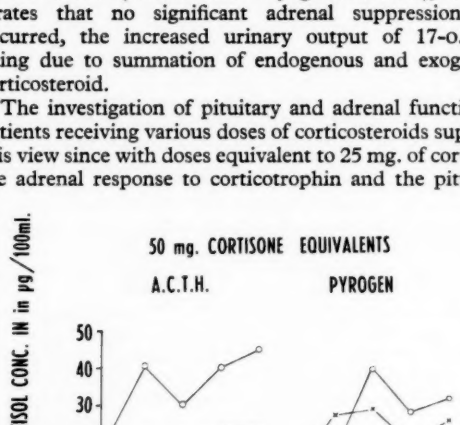

Fig. 5—Response to A.C.T.H. and pyrogen in four patients taking 50 mg. "cortisone equivalents".

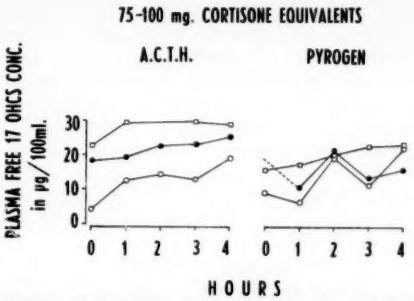

Fig. 6—Effect of A.C.T.H. and pyrogen in three patients taking 15–20 mg. prednisolone.

Results are expressed as free 17-O.H.C.S. for reasons given in the text.

response to pyrogen was normal, although these responses were beginning to decline with doses equivalent to $37^1/_2$–50 mg. of cortisone. In most of the patients receiving larger doses of steroid, the response to corticotrophin appeared to have decreased before the response to pyrogen (e.g., fig. 5). Possibly this indicates a greater sensitivity to endogenous than to exogenous corticotrophin. It seems more probable, however, that the corticotrophin infusion on the previous day had rendered the adrenal more sensitive to the corticotrophin released in response to the pyrogen. This interpretation is in keeping with the observations of Engleman et al. (1953), who found that in patients taking corticosteroids a 3-hour corticotrophin infusion gave a subnormal response whereas the response to a 16-hour infusion was often normal. The present findings are, then, that the first detectable depressant effect on the pituitary-adrenal axis of administered corticosteroid occurs with doses of 37·5 mg. of cortisone or its equivalent. The effect is one of decreased adrenal sensitivity to exogenous corticotrophin and is presumably due to inhibition of pituitary secretion of corticotrophin by the administered corticosteroid.

Although complete lack of pituitary response to pyrogen was observed in one patient who maintained some response to corticotrophin (fig. 5), it is clearly impossible to assess the extent to which the pituitary is unresponsive to pyrogen from changes in plasma-cortisol concentration at a time when the adrenals do not respond normally to corticotrophin. Furthermore, although a normal adrenal response can be restored by corticotrophin, this hormone may itself reduce pituitary secretion of corticotrophin (Kitay et al. 1959). Although corticotrophin secretion is decreased by large doses of corticosteroids (Sayers and Sayers 1949) and increased after adrenalectomy (Sydnor and Sayers 1954), the present data are in keeping with the view that day-to-day changes in plasma-cortisol concentration play little or no part in the regulation of corticotrophin secretion (Ganong and Forsham 1960). The alternative explanation—that cortisone and synthetic corticosteroids are less able to inhibit corticotrophin secretion than are equivalent anti-inflamatory doses of cortisol—appears unlikely, since corticotrophin inhibition and antiinflamatory activities probably run in parallel (Christy et al. 1956).

A steroid withdrawal syndrome occurs in patients who have stopped corticosteroid therapy (Slocumb 1953), and this resembles the syndrome after bilateral adrenalectomy for Cushing's syndrome (Sprague et al. 1953, Skanse et al. 1956). Although both the pituitary and the adrenal may not respond normally to stimulation in patients who have been taking corticosteroids (Engleman et al. 1953, Fredell et al. 1955, Bissell et al. 1959, Liddle et al. 1959, Holub et al. 1959, Ferriman and Page 1960), Amatruda et al. (1960) have found normal pituitary and adrenal function in patients with the steroid withdrawal syndrome. Similarly our observation of normal pituitary and adrenal function in patients taking 25 mg. " cortisone equivalents " suggests that, when this syndrome occurs after withdrawal of small doses of corticosteroids, it is not due to an abnormality either of the pituitary or of the adrenal, and we have in fact found normal plasma-cortisol concentrations in two such patients with this syndrome. Any explanation of the steroid withdrawal syndrome must therefore take the following into account: (1) that it occurs after withdrawal of corticosteroids and after adrenalectomy for Cushing's syndrome; (2) that it responds to corticosteroids; (3) that pituitary-adrenal function may be normal.

These facts could be accounted for if it is supposed that corticosteroids are true drugs of addiction (as defined by Tatum and Seevers 1931), in that, like morphine (Wikler 1950), their withdrawal induces certain physical changes. Thus, even though plasma-cortisol concentrations are normal, the tissues are relatively deficient. The pituitary does not respond to this tissue deficiency, although pituitary and adrenal function may be normal, presumably because there is no added stimulus to corticotrophin release.

The advantage of using small doses of corticosteroids when treatment is prolonged is well appreciated, for the incidence and severity of side-effects is proportional to the dose and the time for which it is given. The present findings provide another reason for doing so since pituitary and adrenal function appear to remain normal during long periods of treatment with 25 mg. of cortisone or its equivalent. The fear that doses of this order were unlikely to be therapeutically effective (*Lancet* 1956) arose from the assumption, now shown to be incorrect, that they would suppress endogenous secretion of cortisol.

Summary

Pituitary-adrenal function was studied during administration of small doses of corticosteroids.

Two groups of patients were studied. In the first group urinary 17-O.H.C.S. metabolites were measured before and during administration of small doses of cortisone (12·5–37·5 mg.). The second group consisted of controls (not taking corticosteroids) and patients who had been taking corticosteroids for an average of 26 months. This dose was therapeutically adequate in all and had not been altered for an average of 15 months.

In this group the pituitary response to intravenous pyrogen and the adrenal response to a 4-hour infusion of corticotrophin were compared by changes in the plasma-cortisol concentration.

Pituitary and adrenal function were found to be normal with doses of 25 mg. " cortisone equivalents " and were depressed to a varying degree in patients taking 37·5–50 mg. per day.

It is suggested that the therapeutic efficiency of small doses of corticosteroids is due to summation of exogenous and endogenous steroid, since small doses do not suppress secretion of cortisol by the adrenal.

The mechanism of the steroid withdrawal syndrome is discussed in the light of the finding of normal pituitary-adrenal function during therapy with small doses of corticosteroid, and the suggestion is made that corti-

costeroids are true drugs of addiction in that they lead to physical dependence.

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REFERENCES

Amatruda, T. T., Hollingsworth, D. R., D'Esopo, N. D., Upton, G. V., Bondy, P. K. (1960) *J. clin. Endocrin.* **20**, 339.
Bissell, G. W., Scott, A. L., Farnsworth, W. E., Winkler, I. (1959) *N.Y. St. J. Med.* **59**, 3596.
Bush, I. E., Sandberg, A. A. (1953) *J. biol. Chem.* **205**, 783.
Christy, N. P., Wallace. E. Z., Jailer, J. W. (1955) *J. clin. Invest.* **34**, 899.
— — (1956) *J. clin. Endocrin.* **16**, 1059.
Conn, J. W., Fajans, S. S., Louis, L. H., Seltzer, H. S., Kaine, H. D. (1954) *Rec. Prog. Horm. Res.* **10**, 471.
Eik-Nes, K., Sandberg, A. A., Nelson, D. H., Tyler, F. H., Samuels, L. T. (1954) *J. clin. Invest.* **33**, 1502.
Engleman, E. P., Krupp, M. A., Johnson, H. P., Welsh, J. E., Wrenn, H. T., King, W. R. (1953) *Arch. intern. Med.* **91**, 1.
Ferriman, D., Page, B. (1960) *Lancet*, ii, 410.
Fredell, E. W., Johnson, H. P., Krupp, M. A., Engleman, E. P., McGrath, A. K. (1955) *Arch. intern. Med.* **95**, 411.
Ganong, W. F., Forsham, P. H. (1960) *Annu. Rev. Physiol.* **22**, 579.
Hatfield, C. B., Shuster, S. (1959) *J. clin. Path.* **12**, 140.
Holub, D. A., Jailer, J. W., Kitay, J. I., Frantz, A. G. (1959) *J. clin. Endocrin.* **19**, 1540.
Ingle, D. J., Kendall, E. C. (1937) *Science*, **86**, 245.
Kitay, J. I., Holub, D. A., Jailer, J. W. (1959) *Endocrinology*, **64**, 475.
Lancet (1956) i, 325.
Liddle, G. W., Estep, H. L., Kendall, J. W., Williams, W. C., Townes, A. W. (1959) *J. clin. Endocrin.* **19**, 875.
Peterson, R. E., Karrer, A., Guerra, S. L. (1957) *Analyt. Chem.* **29**, 144.
— Wyngaarden, J. B. (1956) *J. clin. Invest.* **35**, 552.
Sayers, G. (1950) *Physiol. Rev.* **30**, 241.
— Sayers, M. A. (1949) *Ann. N.Y. Acad. Sci.* **50**, 522.
Silber, R. H., Porter, C. C. (1954) *J. biol. Chem.* **210**, 923.
Skanse, B., Gydell, K., Wulff, H. B., Koch, F. (1956) *Acta. med. scand.* **154**, 119.
Slocumb, C. H. (1953) *Proc. Mayo Clin.* **28**, 655.
Sprague, R. G., Kvale, W. F., Priestley, J. T. (1953) *J. Amer. med. Ass.* **151**, 629.
Sydnor, K. L., Sayers, G. (1954) *Endocrinology*, **55**, 621.
Tatum, A. L., Seevers, M. H. (1931) *Physiol. Rev.* **11**, 107.
Wexler, B. C., Dolgin, A. E., Tryczynski, E. W. (1957) *Endocrinology*, **61**, 300.
— — Zaroslinski, J. F., Tryczynski, E. W. (1958) *ibid.* **63**, 201.
Wikler, A. (1950) *Pharmacol. Rev.* **2**, 435.

INTERMITTENT POSITIVE-PRESSURE RESPIRATION IN TETANUS NEONATORUM

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THE method of treating tetanus by means of total curarisation and intermittent positive-pressure respiration (I.P.P.R.), which was introduced by Danish workers (Bjørnboe et al. 1953), has been successfully used in children and adults with tetanus (Ablett 1956, Glossop and Low 1957, Smith 1958, Lawrence and Sando 1959) and in tetanus neonatorum (Smythe and Bull 1959), but there are no comparative studies. In previous trials we showed that no significant reduction in mortality-rate follows the use of the phenothiazine derivatives chlorpromazine and acetylpromazine, although both appeared to be useful drugs (Laurence et al. 1958, Adams et al. 1959, Wright 1960a). Recently we have used I.P.P.R. for treating neonatal and non-neonatal tetanus in two randomised clinical trials, comparing this method with combinations of chlorpromazine or acetylpromazine and barbiturates. We record here the results of a trial on 50 patients with severe tetanus neonatorum in which we demonstrate that I.P.P.R. significantly lowers the mortality-rate. The results of the trial in non-neonatal tetanus will be reported later.

Design of Trial

Neonatal patients were admitted to the trial only if they were observed by two of us to have frequent and severe spasms, and if permission for tracheotomy had been obtained. They were then allotted at random to one of two groups, which were treated in separate rooms, each with its own complement of nurses. All were given 50,000 units of anti-tetanus serum and penicillin intramuscularly; feeding and management were standardised, as in our previous trials; and in the second half of the trial 2 ml. γ-globulin was given to all patients.

In the *conservative* group, spasms were controlled by acetylpromazine in 22 patients (5–10 mg., usually twice daily), and by chlorpromazine in 3 (12·5 mg. six-hourly) with phenobarbitone sodium (30–60 mg.) added when necessary. All three drugs were given intramuscularly. We have found the results of treatment with acetylpromazine and chlorpromazine to be similar (Wright 1960a).

The technique used in those treated by *I.P.P.R.* has been described previously by one of us (Sykes 1960a), and we shall only summarise the details here. After initial paralysis with suxamethonium (20 mg.), the trachea was intubated and respiration maintained by means of a Radcliffe mark 5 or a Smith-Clarke respirator. Humidified air was used, enriched with oxygen when necessary, and ventilation was controlled by clinical assessment and by measurement of the arterial pCO_2 with a rebreathing technique (Sykes 1960b). Total paralysis was maintained by the intermittent injection of 3 mg. *d*-tubocurarine intramuscularly, the maximum daily dose ranging from 6 mg. to 48 mg. Initial inflation pressures were between 10 and 15 cm. water, but higher pressures were later required in some cases. Tracheotomy at the level of the second, third, and fourth tracheal rings was performed within twenty-four hours of admission, and a shortened size 0 or 00 plain latex armoured tube inserted. This was held in position by a brass clamp and padded harness (Sykes 1960a). Vigorous physiotherapy to the chest and tracheal aspiration were performed hourly or more frequently if secretions were profuse.

As in non-neonatal tetanus we have found that some patients with tetanus neonatorum have characteristic rigidity but reflex spasms are either absent (mild tetanus) or infrequent (moderate tetanus). In this group, which comprised less than 20% of 217 infants with tetanus neonatorum previously treated in this unit, the mortality is low (31%). We excluded such patients from the present trial, admitting only infants in whom we observed frequent and severe reflex spasms—a group in which our own mortality-rate previously was over 90%.

Results

Analysis of the records of the 25 patients in each treatment group with regard to the other two main prognostic criteria—the incubation period, and the time interval

TABLE I—COMPARISON OF TREATMENT GROUPS

—	I.P.P.R.	Conservative
No. of cases	25	25
Average age (days)	6	6·6
Average incubation period (days)	4·9	5·4
Average period of onset (hr.)	5·9	5·9
Average admission-time (hr.)	19·5	25·0
Premature infants (under 5½ lb.)	6	4
Deaths	11	21
Mortality-rate (%)	44	84

*Dr. Sykes visited Durban in 1959 on a grant from the Wellcome Trust.

TABLE II—MORTALITY-RATES IN PREVIOUS SERIES

Series	No. of cases	Mortality (%)
Loh Siew Gek (1951)	174	92
Pinheiro (1957)	256	84
Tompkins (1958)	141	89·6
Wright (1960b)	217	82·5

between the first symptom and the first reflex spasm (" period of onset ")—shows that they are comparable (see table I). The groups are also similar in respect of average age. Patients in the conservative group were admitted to the unit somewhat longer after the first symptom of tetanus (" admission-time ") and there were fewer premature infants than in the I.P.P.R. group.

21 infants died among those treated conservatively—a mortality-rate of 84%. This is similar to the mortality-rates in patients previously admitted to the unit and to those published in other large series (see table II).

1 infant in the I.P.P.R. group still has the tracheotomy tube in situ after thirteen months, but recovery was complete in 13. 11 have died, giving a mortality-rate of 44%. The difference between the two rates is statistically significant ($P < 0.1$).

Causes of Death

At necropsy in cases of tetanus the cause of death is not always apparent. Changes observed, such as bronchopneumonia and pulmonary collapse, unless they are gross, are probably only contributing causes; in many cases the main cause of death may be tetanus intoxication of the medullary centres.

In the *conservative* group bronchopneumonia or pulmonary collapse was observed in half the patients, with cerebral hæmorrhage in 1 of them. Another had intrathoracic hæmorrhage, and in 2 there were no gross changes.

In the I.P.P.R. group death could usually be attributed in varying degree to faulty technique. 6 of the deaths occurred among the first 8 patients; at necropsy 4 of these showed gross bronchopneumonia, 1 patient died of asphyxia at 29 days and another of gastroenteritis at 34 days. In these early cases, death often followed dislodgment of the tracheotomy tube or gross bilateral pneumonia, the infection probably being introduced from unfiltered air or during suction of trachea and bronchi. Once adequate immobilisation of the tracheotomy tube had been achieved and a sterile suction technique perfected there was a considerable improvement in results, with only 5 deaths among 17 patients. 3 died of asphyxia at 16, 41, and 45 days. In 2 patients, 1 of whom had lateral-sinus thrombosis, death was preceded by generalised flaccid paralysis similar to that described by Smythe and Bull (1959) and Stirnemann and Bronniman (1957).

Discussion

Our previous work suggested that the main causes of death in tetanus neonatorum were inadequate control of reflex spasms, bronchopneumonia, and respiratory failure of central origin. We embarked on this trial because we thought that total paralysis and intermittent positive-pressure respiration would abolish the first of these causes of death and at least minimise the effects of the other two. We felt justified in conducting a comparative trial of this nature since no treatment had previously proved effective.

It soon became apparent that bronchopneumonia could be prevented only by scrupulous attention to detail. Masks were worn in the unit, and particular care was taken to ensure that the suction technique was aseptic. In the prevention of chest complications, besides these factors, humidification of the inspired air and regular physiotherapy are essential. Recognition of pneumonia in an infant on the respirator is sometimes difficult, but we have observed that the secretions aspirated often change from mucoid to purulent before there are clinical or radiological signs.

Another problem we faced was how long we should maintain respiration mechanically. In the spinal cord the main effect of tetanus toxin wears off in two to three weeks as judged by the cessation of reflex spasms and the diminution of rigidity. If the assumptions are correct that the toxin may also affect the medullary centres and that it behaves here much as it does in the cord, then artificial respiration should be maintained for two to three weeks. Smythe and Bull (1959) kept some of their patients on the respirator only for short periods. Curare was given for twenty-eight days in our 1st patient, but twelve to sixteen days was later considered to be the optimum period; in no patient was it discontinued before the eleventh day. In the early part of the trial attempts were made to replace the curare with sedation at intervals of two or three days. When spasms were adequately controlled and no curare had been given for eight to twenty-four hours, the infant was removed from the respirator for increasing periods and allowed to breathe spontaneously. When necessary, respiration was assisted by manual inflation with oxygen. In the second half of the trial a technique of " assisted respiration " was introduced by one of us (Jackson 1961). Curare was stopped somewhat earlier than previously but respiration was still assisted mechanically for some days. The rate of the respirator was reduced and one limb of the suction connector was opened to the air, enabling the infant to breath spontaneously between inflations with the respirator. We believe that " assisted respiration " reduced the complications and dangers of the weaning period. Nevertheless apnœic attacks were still a danger during the third and fourth weeks when rigidity had returned and spontaneous respiration was being established.

Once sucking had commenced, either from breast, bottle, or Belcroy feeder, attempts were made to remove the tracheotomy tube. The type of opening made in the trachea seems to determine the ease with which the tube can be permanently removed. In the first half of the series a window was cut in the trachea; in 3 infants the tube could be removed only after many months (a hundred and forty to two hundred and twenty-seven days), while in another the tracheotomy tube is still in situ after four hundred days. In the latter part of the trial a vertical incision through the tracheal rings enabled us to remove the tube within three weeks in all cases. When considerable difficulty occurred we found it advisable to allow the infant to outgrow the tracheotomy, short attempts at spontaneous respiration without the tube being allowed periodically to assess progress.

During the period of total paralysis we often encountered œdema and hypothermia; and sometimes there was constipation and even paralytic ileus. Œdema in varying degree frequently developed in the first two days and was more severe than in conservatively treated infants. The cause is obscure. Constipation is a notable feature in most cases treated on the respirator, so careful observation and annotation of bowel movements is imperative. When the

volume of gastric feeds during the initial period of total paralysis is too great, gastric stasis may occur and paralytic ileus follow, for which intravenous feeding is indicated. To minimise these risks we aspirate the stomach contents by indwelling tube before each feed, giving the full amount only if there is no residue. If an aspirate is obtained, we measure it and return it to the stomach with the balance of the feed; but we omit the feed if the gastric contents appear excessive.

These results leave no doubt about the superiority of total paralysis and I.P.P.R. over the conservative method used in severe cases of tetanus neonatorum. The mortality-rate using I.P.P.R., however, remains higher than in "mild" or "moderate" cases treated conservatively; so it is essential to assess the severity of the disease by careful observation of the patient before deciding on the method of treatment. We do this by watching for reflex spasms and noting their frequency without disturbing the patient; severe cases, comprising the majority in tetanus neonatorum, will usually have a number of spasms over a ten-minute period, but in others spasms only become severe and frequent within the next few hours. At present only severe cases should be treated by I.P.P.R. Moreover we hesitate to recommend this method for treating isolated cases, even when severe, because we found that the death-rate was high early on in the trial while the technique was being perfected. In countries where tetanus neonatorum is common only improved maternity services will eliminate the disease, but meanwhile special respiratory units set up in regional centres could do much to reduce the death-rate.

Summary

In a randomised clinical trial on 50 infants with severe tetanus neonatorum, total curarisation and intermittent positive-pressure respiration was shown to be superior to conservative treatment using phenothiazine derivatives and phenobarbitone to control spasms.

This study was made possible by generous grants from the Wellcome Trust. We are indebted to Mr. R. Gowans, F.R.C.S.E., and his staff for the tracheotomies; and to Prof. J. Wainwright and his colleagues in the department of pathology for performing the necropsies and examining histological sections. We also thank Dr. S. Disler, medical superintendent, King Edward VIII Hospital, for facilities; the matron and nursing staff for their help; and Benger Laboratories Ltd. for supplying us with acetylpromazine.

REFERENCES

Ablett, J. J. L., (1956) *Brit. J. Anæsth.* **28**, 258.
Adams, E. B., Wright, R., Berman, E., Laurence, D. R. (1959) *Lancet*, i, 755.
Bjørnboe, M., Ibsen, B., Johnsen, S. (1953) *Ugeskr. Laeg.* **115**, 1535.
Glossop, M. W., Low, M. D. W. (1957) *Brit. J. Anæsth.* **29**, 326.
Jackson, B. G. (1961) Unpublished.
Laurence, D. R., Berman, E., Scragg, J. N., Adams, E. B. (1958) *Lancet*, i, 987.
Lawrence, J. R., Sando, M. J. W. (1959) *Brit. med. J.* ii, 113.
Loh Siew Gek (1951) *Med. J. Malaya*, **5**, 181.
Pinheiro, D. (1957) *J. Pediat.* **51**, 171.
Smith, A. C. (1958) *Proc. R. Soc. Med.* **51**, 1006.
Smythe, P. M., Bull, A. (1959) *Brit. med. J.* ii, 107.
Stirnemann, H., Bronniman, R. (1957) *Arch. klin. Chir.* **286**, 335.
Sykes, M. K. (1960a) *Anæsthesia*, **15**, 401.
— (1960b) *Brit. J. Anæsth.* **32**, 256.
Tompkins, A. B. (1958) *Brit. med. J.* i, 1382.
Wright, R. (1960a) *Trans. R. Soc. trop. Med. Hyg.* **54**, 270.
— (1960b) *S. Afr. med. J.* **34**, 111.

Addendum

We have subsequently used total curarisation and I.P.P.R. to treat 18 other infants suffering from severe tetanus neonatorum, with only 2 deaths (mortality-rate 11%). The mean incubation period (5·8 days) and period of onset (12·3 hours) were somewhat longer than in the trial. The tracheostomy tube was successfully removed in all the survivors.

INFLUENCE OF INCREASED OXYGENATION ON INFLUENZA VIRUS INFECTION IN MICE

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RECENTLY there has been growing evidence that interferon may play an important part in recovery from virus infections. Evidence comes firstly from the close correlation between the onset of recovery of mice from influenzal pneumonia (Isaacs and Hitchcock 1960) or from arborvirus infection of the mouse brain (Hitchcock and Porterfield 1961) with the time of appearance of interferon but not antibody. Secondly, Enders (1960) has reported that attenuated strains of measles produce larger quantities of interferon than do virulent strains. And thirdly, in the chick embryo, a close correlation has been observed between sensitivity to interferon at different ages and ability to survive virus infections (Baron and Isaacs 1961).

In these experiments the evidence suggests that antibody has a less important role in recovery from virus infections than has often been assumed in the past. The normal response to virus infections of patients with hypogammaglobulinæmia (Gross et al. 1959) and the normal recovery from vaccinial infection of guineapigs which were unable to produce antibody after X-irradiation (Friedman and Baron 1961) give further support to the concept that antibody plays a lesser part in recovery; the same point was stressed recently by Lwoff and Lwoff (1960).

In the course of experiments with different viruses grown in vitro, it was found that under increased oxygen tension the antiviral action of interferon was greatly reduced (Isaacs, Porterfield, and Baron 1961) and, possibly as a result, virus growth was enhanced (Baron, Porterfield, and Isaacs 1961). If interferon helps animals to recover from virus infections one might expect that animals kept under increased oxygenation might suffer more severe virus infections. The present experiments were designed to test this possibility.

Materials and Methods

Swiss white mice weighing 12–15 g. were infected intranasally with 0·05 ml. volumes of egg cultures of influenza viruses under light ether anæsthesia. Approximately 10^4 egg infective doses of the Lee strain of influenza B or 10^2 egg infective doses of the WS strain of influenza A were used. After infection, groups of mice were kept in airtight 'Perspex' boxes ($27 \times 27 \times 40$ cm.). A mixture of approximately equal parts of oxygen and nitrogen was blown into the box and the gas stream let out through an open outlet. Other groups of infected mice were kept in tin cages in the normal atmosphere. In some later experiments the non-oxygenated mice were kept in airtight perspex boxes and flushed with air from a compressor. During the early experiments uninfected mice were oxygenated along with the infected ones in the same boxes.

The mice were observed for periods of ten to twelve days; the number of dead animals was recorded daily; and they were checked for typical lung lesions.

The results are presented as cumulative percentages of mortality in the oxygenated and non-oxygenated groups.

Results

From previously published findings (Bean 1945) it was expected that 50% oxygen would not prove to be toxic, and

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in the present experiments oxygenated uninfected mice did not die, nor did their lungs show any gross morphological changes when they were killed after oxygenation for twelve days.

In preliminary experiments it appeared that mice infected with the Lee strain of influenza virus B and kept in 50% oxygen died earlier than mice similarly infected and kept in air. The final mortality was also higher in the oxygen mice (see fig. 1). Fig. 2 shows that mice infected with the WS strain of influenza virus A behaved similarly, although the differences between the oxygen and air groups were less pronounced than with the virus B.

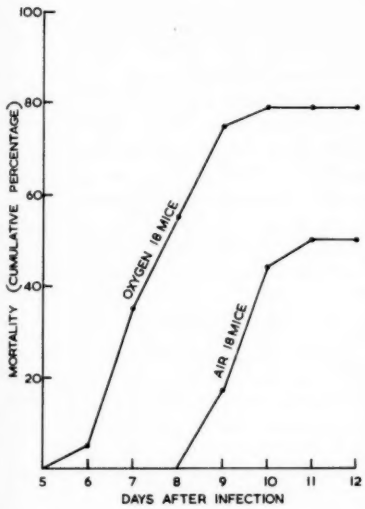

Fig. 1—Mortality of mice infected with influenza virus B (Lee) and maintained in 50% oxygen or air.

In further experiments with influenza virus B, additional controls were included. In these, a third group was added consisting of mice kept in the same type of perspex box as the oxygen mice but with air blown through instead of 50% oxygen. The results of an experiment of this kind are shown in fig. 3. It will be seen that the mice with air blown through the box showed a mortality that was intermediate between that of the oxygen mice and the mice kept in tins without air being blown through. At first, an effect of humidity was suspected, since the air and the 50% oxygen and nitrogen were bubbled through water. But in a further experiment, in which two perspex boxes were used, one aerated with "dry" and the other with "wet" air, no differences in mortality-rates were seen between these two groups. At present therefore we cannot explain why mice kept in the box with air blown through should have a higher mortality than the mice kept in tins.

Fig. 4 shows the effect of 50% oxygen on infection with influenza B virus in all the experiments combined. In these, 83 mice kept in 50% oxygen are compared with 179 mice kept in either "stationary" or "moving" air, dry or humidified. (The effect of oxygen, although smaller than that shown in fig. 1, nevertheless seems clear.) The increased mortality-rate and increased final mortality resulting from application of an atmosphere of 50% oxygen is highly significant ($P = <0.01$).

Discussion

These experiments show that increased oxygenation, which is known to inhibit the action of

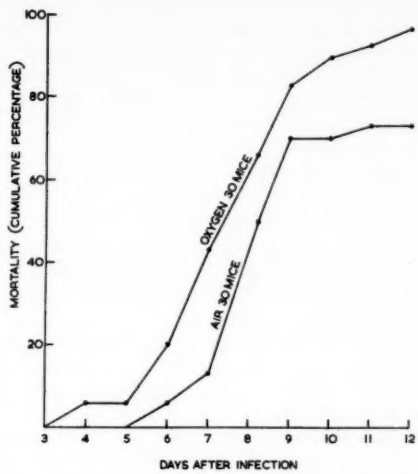

Fig. 2—Mortality of mice infected with influenza virus A (WS) and maintained in 50% oxygen or air.

interferon in vitro, has a harmful effect on mice infected with influenza virus. Consistent with the present results is the previous finding that, in influenzal infection of mice, a lowered oxygen tension had the effect of slowing the rate of virus multiplication (Kalter et al. 1952, 1955) and reducing the mortality of the mice (Berry et al. 1955). While these findings do not demonstrate that the effect of the oxygen is on the interferon mechanism in vivo, the explanation is tempting.

Recently, Smart and Kilbourne (1961) have shown that cortisone inhibits the production and action of interferon in vitro, and there is clinical evidence that patients under treatment with cortisone may suffer severe chickenpox infections which in some cases end fatally (McMath 1959) despite the inability of this amount of cortisone to alter antibody synthesis (Larson and Tomlinson 1951; W. W. Holland and F. O. MacCallum, personal communication). This reinforces the suggestion that inhibition

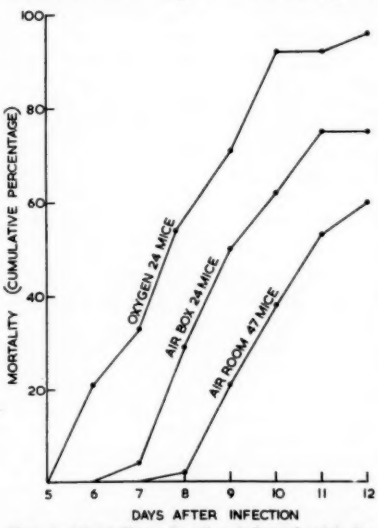

Fig. 3—Mortality of mice infected with influenza virus B (Lee), maintained in 50% oxygen, in boxes with air blown through and in tins.

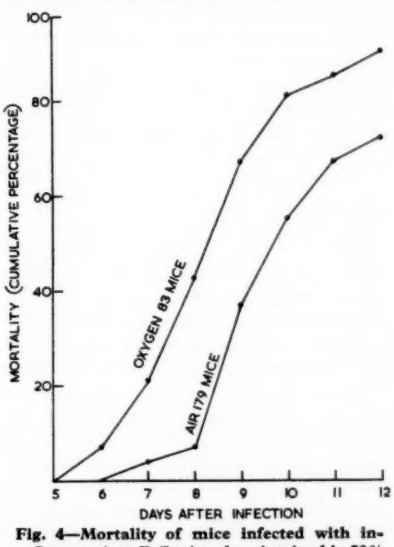

Fig. 4—Mortality of mice infected with influenza virus B (Lee) and maintained in 50% oxygen or air. Results of all the experiments combined.

of the interferon mechanism has a harmful effect in virus infections. The alternative explanation, that oxygen is acting independently of the interferon mechanism, might be tested by observing the effect of oxygen in animals treated with sufficient cortisone to block completely their interferon mechanism. However, from the practical point of view it may be worth re-studying the effect of administered oxygen on infants suffering from viral infections of the respiratory tract.

Summary

Earlier studies in vitro had demonstrated that increased oxygen tension greatly reduced the antiviral action of interferon, which is thought to be important in recovery from viral infections.

Experiments in mice infected with influenza virus have shown an earlier appearance of lethal pneumonia, and an increased final mortality-rate, in animals kept under increased oxygen tension.

We should like to thank Miss Marjory V. Mussett for calculations of the statistical significance of the results. The valuable technical assistance of Mr. A. O. Charles is acknowledged.

REFERENCES

Baron, S., Isaacs, A. (1961) *Nature, Lond.* **191**, 97.
— Porterfield, J., Isaacs, A. (1961) *Virology*, **14**, 444.
Bean, J. W. (1945) *Physiol. Rev.* **25**, 1.
Berry, L. J., Mitchell, R. B., Rubenstein, D. (1955) *Proc. Soc. exp. Biol., N.Y.* **88**, 543.
Enders, J. (1960) *Trans. Coll. Physcns Phila.* **28**, 68.
Friedman, R. M., Baron, S. (1961) *J. Immunol.* (in the press).
Gross, P. A. M., Gitlin, D., Janeway, C. A. (1959) *New Engl. J. Med.* **260**, 170.
Hitchcock, G., Porterfield, J. (1961) *Virology*, **13**, 363.
Isaacs, A., Hitchcock, J. (1960) *Lancet*, ii, 69.
— Porterfield, J., Baron, S. (1961) *Virology*, **14**, 450.
Kalter, S. S., Tepperman, J. (1952) *Science*, **115**, 621.
— Prier, J. E., Zaman, H. (1955) *J. exp. Med.* **102**, 475.
Larson, D. L., Tomlinson, L. J. (1951) *J. clin. Invest.* **30**, 1451.
Lwoff, A., Lwoff, M. (1960) *Ann. Inst. Pasteur*, **98**, 173.
McMath, W. F. T. (1959) *Brit. J. clin. Pract.* **13**, 175.
Smart, M. K., Kilbourne, E. D. (1961) *Fed. Proc.* **20**, 441.

HERPES-SIMPLEX MENINGOENCEPHALITIS

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MOST individuals acquire their primary infection with herpes simplex in childhood, the commonest manifestation being gingivostomatitis. As a result of this infection the individual not only develops antibodies which persist for many years but also carries the virus for life and is liable to recurrent attacks of herpes labialis (Burnet and Williams 1939). A rare manifestation of primary herpetic infection is meningoencephalitis which has been reported from postmortem findings both in infants (Smith et al. 1941, Wildi 1951) and in adults (Zarofonetis et al. 1944, Whitman et al. 1946). In these cases the diagnosis was established by isolation of herpes virus from cerebral tissue obtained at necropsy and in some by the finding of intranuclear inclusion bodies characteristic of herpes infection.

Reports of patients who have survived herpetic infection of the central nervous system have been few. Florman and Mindlin (1952) described a case of generalised herpes in an 11-day-old premature infant who had meningoencephalitis but survived with neurological defects and chorioretinitis. Afzelius-Alm (1951) in Gothenburg, Sweden, found serological evidence of infection with herpes simplex in 11 of 168 cases of meningoencephalitis. Despite serious involvement of the central nervous system in most of these 11 cases during the acute illness, all recovered completely within a few weeks.

The most reliable laboratory evidence of primary herpetic infection is the demonstration of a rising serum-antibody titre during the illness. The serological tests used are neutralisation tests in mice or in embryonated eggs, or complement fixation (C.F.) tests. As neutralisation tests are expensive in time and materials, many workers within recent years have favoured C.F. tests. The C.F. antigen which has been most commonly used has been prepared from chorioallantoic membrane (C.A.M.) of the chick embryo (Hayward 1949, Dudgeon 1950). In primary and recurrent herpes good correlation was found between the results of the C.F. test using C.A.M. antigen and the results of neutralisation tests (Holzel et al. 1953, Sosa-Martinez and Lennette 1955), although Hozel et al. (1953) found that this antigen gave a considerable number of non-specific reactions. On the other hand, other workers could not obtain satisfactory results with C.A.M. antigen (Afzelius-Alm 1951, Balducci et al. 1956).

This paper describes 8 cases of herpes encephalitis or meningoencephalitis in which serological diagnosis was established by the C.F. technique using a C.A.M. antigen. Certain factors affecting the reliability of the antigen were studied.

Materials and Methods

The 8 cases arose during the period from July, 1958, to November, 1960. They all showed signs and symptoms of acute encephalitis or meningoencephalitis. Our definition of encephalitic involvement comprised upper-motor-neurone-type paralysis of cranial nerves, extremities, or trunk, or coma lasting longer than 24 hours. A greater then fourfold rise in C.F. titre to herpes was obtained in each case during the illness.

Preparation of C.F. Antigen

The antigen was obtained by a modification of the method of Sosa-Martinez and Lennette (1955). 0·25 ml. of a 10^{-2} dilution of C.A.M. or yolk-sac suspension of the H.F.E.M. strain of virus, containing approximately 1000 I.D.$_{50}$, was inoculated into the yolk sac of 7-8-day-old embryonated eggs which were incubated at 36°C. Eggs dying before the 40th hour were discarded. Between the 40th and 50th hours, eggs were candled twice and those recently dead or sluggish were placed in a refrigerator and chilled from 4 to 18 hours before harvesting. Chorioallantoic membranes and amniotic sacs were removed, rinsed with saline, and drained. An equal volume of barbitone-buffered saline was added to the membranes which were then homogenised in a M.S.E. masticator at maximum speed for 3 minutes and centrifuged at 2000 r.p.m. for 10 minutes. The supernate constituted the crude antigen.

We found that the reliability of this antigen was much improved by the following modifications:

(*a*) Removal of non-specific reactivity by a fluorocarbon compound (Gessler et al. 1956). To two parts of the above supernate one part of the fluorocarbon Arcton 113 (I.C.I. Ltd.) was added, and the mixture homogenised for 2 minutes. It was then centrifuged at 2000 r.p.m. for 5 minutes; the supernate was again treated with fluorocarbon, centrifuged as before and stored at −40°C.

(*b*) Optimal dilution of each batch of antigen was determined by chessboard titration against positive herpes human serum. Human serum was used in place of type-specific sera prepared in guineapigs because preliminary experiments had shown that the optimal titre of the antigen against guineapig serum was higher than against human serum.

(*c*) Preliminary screen tests with a single dilution of 1 in 8 " convalescent " test sera were done against antigen at three dilutions—namely, optimal dilution as determined by chessboard titration, four times optimal dilution and one-fourth optimal dilution. This was necessary because we found that the optimal dilution of the antigen varied with different human sera, but not between paired sera from one individual. Titrations of each paired sera were then carried out with the dilution of antigen which showed optimal fixation.

Test Sera

These were stored at −20°C before testing. They were then thawed, diluted 1 in 8, and inactivated at 56°C for 30 minutes.

C.F. Test Technique

The tests were carried out in plastic plates with 0·1 ml. volumes each of antigen dilution, serum dilution, and complement (four 50% hæmolytic doses). Dilutions of all reagents were made in barbitone-buffered saline. After standing at 4°C overnight, the plates were kept at 37°C for 30 minutes, and then 0·1 ml. 2% optimally sensitised sheep cells were added to each cup. The plates were left for a further 40 minutes at 37°C, and were shaken at 15, 30, and 40 minutes, and then allowed to settle at room temperature before reading.

Clinical Findings

Group 1

In this group (3 children and 1 adult) despite the apparent severity of neurological involvement during the acute stage of the illness recovery was rapid and apparently complete within a few weeks.

Case 1.—A male infant, aged 9 months, was admitted on Nov. 2, 1958, with a history of vomiting, listlessness, and anorexia for 2 days. He was an ill child with an inflamed throat and signs of bronchitis. Temperature 99°F. A diagnosis of acute respiratory infection was made and penicillin was given. Within a few hours the child became comatose and collapsed. Oxygen, 'Eucortone', and tube-feeding were administered. Next day the child had periods of generalised spasticity alternating with extreme flaccidity, but after 3 days he began to improve. When he was discharged on Nov. 17, recovery seemed complete.

Case 2.—A boy of 2 years was admitted on Oct. 21, 1960, after 3 days' irritability, anorexia, and respiratory catarrh. He had severe gingivostomatitis with cervical adenopathy. 10 days after admission he suddenly had generalised convulsions interspersed with localised twitchings of the right arm and face. He was given phenobarbitone and paraldehyde. An electroencephalogram showed gross changes involving both hemispheres, but mainly the left. Once his convulsions had settled it was apparent that he had right facial weakness and hemiplegia. He recovered quite quickly, however: a repeat E.E.G. a week later showed great improvement. On discharge on Nov. 18, the only residual feature was some emotional lability. On Dec. 9, 1960, he appeared normal.

Case 3.—A boy, aged 3, was admitted on Oct. 6, 1959, in a coma which lasted 3 days. No stomatitis was detected. During this time he had minor epileptic fits and spasms of restlessness with periods of spasticity and crying. Nystagmus was present for the first two days. Tendon reflexes were increased and plantar responses were extensor. He gradually improved until by the 5th day he appeared completely normal. When reviewed 14 months later no abnormality was detected.

Case 4.—A man, aged 25, was admitted on July 6, 1959. He had been ill for 5 days with malaise, sore mouth, and tingling sensations in face, arms, and legs. There was a profuse vesicular eruption on tongue, soft palate, and left tonsil. Some of the vesicles had ruptured leaving shallow ulcers. Cervical glands were enlarged and tender. On July 10, he complained of severe headache, and, on July 12, of pain in the left face. On July 13, he had a severe bilateral facial-nerve paralysis which gradually disappeared in a week. On discharge, on Aug. 8, he had made a full recovery. Before and during the patient's illness his three children (aged 2 months, 1 year, and $2^1/_2$ years) and his wife had gingivostomatitis.

Group 2

In this group (1 child and 2 adults) recovery was very slow, and neurological and mental sequelæ were still present a year or more after the acute illness.

Case 5.—A boy, aged 14 months, was admitted on July 12, 1958. His illness began the previous day with vomiting, irritability, and frequent convulsions. He had two small ulcers on the palate. There was a mild hemiparesis. He remained pyrexial (up to 102°F) for 7 days. He gradually improved, and was discharged apparently well on Aug. 6. He was readmitted on Aug. 11 with an acute choreiform illness, consisting of hyperkinesia and constant writhing movements. Temperature reached 102°F. Mild left hemiparesis and left hemianopia were detected. Tendon reflexes could not be elicited in his left arm but otherwise they were normal: left plantar reflex was extensor. An E.E.G. showed generalised high-voltage, very slow activity on both sides. He was given sedatives and cortisone. The child gradually improved, but on discharge on Oct. 14 there was still a mild left-sided hemiparesis and left hemianopia, and his activity was rather purposeless. He was best controlled on phenobarbitone and primidone which were continued at home. When last reviewed 2 years later he was still hyperkinetic. He had an alternating internal squint and showed some degree of mental retardation.

Case 6.—A female, aged 28, was admitted on Sept. 29, 1959. Her illness began 4 days earlier with severe headaches and vomiting, followed by drowsiness and, on the day of admission, by inability to speak properly and dragging of her right leg. On admission she was semi-comatose. No stomatitis was noted. There was gross dysphasia, increased tendon jerks with spasticity of right leg, and early papilloedema. She was transferred to a neurological unit where investigations for a space-occupying lesion were all negative. She ran an intermittent temperature for 4 weeks, and when her temperature settled she still had considerable dysphasia and dementia. Cortisone was given. There was some slow improvement over the next 4 months, but on discharge home in care of her mother, on Feb. 3, 1960, she still showed gross organic dementia. When reviewed in January, 1961, there was no apparent improvement.

Case 7.—A female, aged 46 became ill on Nov. 11, 1958, with fever, headache, and vomiting. On Nov. 18, an itchy skin eruption developed on her forehead and spread to the face, trunk, and limbs. Convulsions began next day, associated with episodes of hyperventilation. She was admitted on Nov. 20, in coma which lasted for about 24 hours, and then developed periodic convulsions associated with episodes of hyperventilation which were followed by deviation of the head to the left and twitching of the face and limbs. No stomatitis was detected during her illness. Since then, she has had postencephalitic epilepsy which is controlled by phenobarbitone and phenytoin sodium.

Group 3

The single fatal case was the youngest in the series.

Case 8.—A male infant, aged 6 months, was admitted on Oct. 10, 1958, with a 4-day history of vomiting, irritability, and listlessness. There was marked injection of the throat, signs of bronchopneumonia, and severe nuchal rigidity with a bulging fontanelle. Temperature was 102°F. A diagnosis of bronchopneumonia was made and treatment with penicillin and later chloramphenicol was given, but response was poor. The temperature rose to 104°F and the onset of generalised convulsions ended in coma. By Nov. 1, there was some improvement: the fever had settled and convulsions had ceased, though generalised spasticity continued. On Nov. 9, the condition suddenly deteriorated with pulmonary œdema and high fever. The child died on Nov. 11. Necropsy showed extensive destruction of grey matter in brain and cerebellum, but no intranuclear inclusion bodies could be detected histologically.

Laboratory Findings

The relevant laboratory findings are shown in the accompanying table.

C.F. Titres of Sera

The size of the C.F. antibody response to herpes bore no apparent relationship to the outcome of the disease. Consideration of the titres of the first specimens from each patient, taken between the 3rd and 8th days of illness,

C.S.F. FINDINGS IN HERPES MENINGOENCEPHALITIS

Case	Age (yr.)	Sex	Serum		Highest C.S.F. cell count (per c.mm.)
			Day of illness	Herpes C.F. titre	
Group 1: Rapid recovery					
1	9/12	F	3	<16	53
			25	128	
2	2	M	5	<8	10
			12	256	
			55	16	
3	3	M	2	16	5
			18	128	
			1 yr.	16	
4	25	M	2	<8	20
			17	64	
			30	32	
Group 2: Residual sequelæ					
5	1	M	5	128	358 (a)
			22	1024	11 (b)
			2 yr.	256	
6	28	F	5	16	58
			22	128	
			37	128	
7	46	F	8	<8	4
			22	32	
			30	32	
Group 3: Fatal					
8	6/12	F	5	<16	30
			14	512	

showed that, with the exception of case 5, the C.F. titres were 16 or less. When the second specimens were taken, from the 12th to 25th days, there had been a fourfold or greater rise in titre. This rise from a low level is in keeping with primary development of herpetic antibodies. That no rise in titre occurs in recurrent herpetic infections has been reported by various workers (Dudgeon 1950, Holzel et al. 1953). To find out if a recurrent herpetic infection developing in the course of another infection might cause a rise in the herpes serum titre, we examined paired sera from 14 individuals with herpes, aged from 2 to 70, who developed herpes labialis while in hospital with various pyrexial illnesses. In no case was a fourfold or greater rise in C.F. titre obtained.

Cerebrospinal Fluid Cell Count

There was a lymphocytic pleocytosis of the C.S.F. in 6 of the 8 patients (cases 1, 2, 4, 5, 6, and 8) in whom the illness may therefore be described as meningoencephalitis. The total count, however, was below 60 cells per c.mm., except in case 5 whose cell count was high during the first phase (a) but had fallen to 11 per c.mm. during the second phase (b) of the illness.

Discussion

Herpetic infection of the central nervous system may manifest itself clinically as aseptic meningitis, encephalitis, or meningoencephalitis. In any attempt to assess the relative importance of herpes in these three categories it must be emphasised that although aseptic meningitis and meningoencephalitis, with lymphocytic pleocytosis in the C.S.F. from which no bacteria have been isolated, are usually due to viral infection, no such claim can be made for encephalitis since vascular, toxic, or metabolic disorders may cause encephalitic signs and symptoms. In this study 6 cases presented as meningoencephalitis and 2 as encephalitis. The 6 cases of herpes meningoencephalitis formed a considerable proportion (19·3%) of a total of 31 cases of meningoencephalitis from whom we received paired sera during the course of this study. During the same period we also examined paired sera from 330 cases of aseptic meningitis without evidence of encephalitis: only 2 (0·6%) showed rising titres for herpes, and both were infants under 1 year of age. Although the number of our herpes cases is small it seems that when herpes simplex invades the central nervous system meningoencephalitis occurs more frequently than aseptic meningitis.

In this series, with the exception of case 5, evidence of encephalitis did not appear until some time after admission, varying from several hours to 10 days. (Case 5 showed a biphasic neurological illness with transient involvement of the central nervous system in the first phase and severe permanent involvement in the second phase). That herpetic infection was present on admission might be deduced from the finding of stomatitis or " inflammation of the throat " in 5 of the 8 cases. This suggests that the encephalitis was a late manifestation of the primary illness.

Although demonstration of a rising antibody titre for herpes suggested that the encephalitis was part of a primary herpetic infection, dual infection was also a possibility—a primary herpetic stomatitis might precede or coincide with some other viral infection which was responsible for the encephalitis. However, serological examination by C.F. tests showed no high or rising titres for mumps, lymphocytic choriomeningitis, adenovirus, louping ill, or influenza types A, B, or C. Specimens of fæces (from cases 1, 2, 5, 6, 7, and 8) and C.S.F. (from cases 1, 2, 4, 6, and 7) were examined for viruses by inoculation of amnion and/or monkey-kidney tissue cultures and suckling mice. A virus was isolated only from the fæces of case 2: this virus has not yet been identified as it was not poliomyelitis types 1, 2, or 3, Echo types 1 to 20, Coxsackie B1 to B6, Frater (Duncan 1960): nor was it pathogenic for suckling mice. It seems therefore that the encephalitis in these cases was not associated with a commonly recognised virus. Our failure to isolate herpes simplex from these specimens must also be noted. Although our methods of stool extraction were suitable for enteroviral isolations, however, they were not optimal for isolation of the more labile herpes virus. Failure to isolate herpes from the specimens of C.S.F. may be in keeping with the low cellular response of the C.S.F., since this suggests that there was little or no virus in the fluid at the time of collection.

That age has an important influence on the manifestations of primary herpetic infection has been demonstrated by various workers. In the neonatal period and in young infants herpes can cause a rapidly fatal infection with generalised visceral involvement (Zuelzer and Stulberg 1952). Such infection is generally ascribed to lack of maternal antibody, although MacCallum (1959) has shown that in some infants who died from herpes infection there was no quantitative deficiency in herpetic antibody. Burnet and Williams (1939) postulated a non-antibody resistance to herpes which developed some time in childhood and which divided the population in two groups, herpetics and non-herpetics. That the resistance of the non-herpetic is relative is suggested by case 4 in the present series who acquired a primary infection when subjected to a high concentration of infection from close contact with young children. Again, a study of the distribution of C.F. herpes antibody at different ages by Holzel et al. (1953) has shown that although primary herpetic infection predominantly occurred in children it was also found in adults. Of the 8 cases, 3 were adults—a rather high proportion: 2 of the 3 adults had severe residual sequelæ compared with 1 of the 4 children who survived. This would suggest that, when primary infection does occur in adults, involvement of the central nervous system is more common and is more severe than in children.

Summary

6 cases of herpes-simplex meningoencephalitis and 2 cases of encephalitis were all diagnosed as primary herpetic infections by serological demonstration of a greater than fourfold rise in C.F. antibody titre for herpes using a chorioallantoic membrane antigen. Certain factors affecting the reliability of the antigen were studied.

4 patients made a rapid and apparently complete recovery within a few weeks. 3 recovered very slowly and showed residual neurological or mental sequelæ a year or more after the acute illness. The youngest patient died.

Stomatitis, when present, preceded clinical evidence of encephalitis by several days.

Herpetic involvement of the central nervous system resulted in proportionately more cases of meningoencephalitis than of aseptic meningitis. The C.S.F. cell count was below 60 per c.mm. in most cases.

Our findings suggest that primary herpetic infection of the adult may result in more meningoencephalitis than in childhood, and that residual neurological and mental sequelæ may be more common.

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REFERENCES

Afzelius-Alm, L. (1951) *Acta med. Scand.* **263**, 1.
Balducci, D., Tyrrell, D. J., Stuart-Harris, C. H. (1956) *Arch. Virusforsch.* **7**, 28.
Burnet, F. M., Williams, S. W. (1939) *Med. J. Aust.* i, 637.
Dudgeon, J. A. (1950) *J. clin. Path.* **3**, 239.
Duncan, I. B. R. (1960) *Lancet*, i, 470.
Florman, A. L., Mindlin, R. L. (1952) *Amer. J. dis. Child.* **83**, 481.
Gessler, A. E., Bender, C. E., Parkinson, M. C. (1956) *Trans. N.Y. Acad. Sci.* **18**, 701.
Hayward, M. E. (1949) *Brit. J. exp. Path.* **30**, 520.
Holzel, A., Feldman, G. V., Tobin, J. O'H., Harper, J. (1953) *Acta. pediat.* **42**, 206.
MacCallum, F. O. (1959) *Acta virol.* **3**, 17.
Smith, M., Lennette, E. H., Reames, H. R. (1941) *Amer. J. Path.* **17**, 55.
Sosa-Martinez, J., Lennette, E. H. (1955) *J. Bact.* **70**, 205.
Whitman, L., Wall, M. J., Warren, J. (1946) *J. Amer. med. Ass.* **131**, 1408.
Wildi, E. (1951) *Rev. neurol.* **84**, 201.
Zarofenitis, C. J. D., Smadel, J. E., Adams, J. W., Haymaker, W. (1944) *Amer. J. Path.* **20**, 429.
Zuelzer, W. W., Stulberg, C. S. (1952) *Amer. J. dis. Child.* **83**, 421.

SUBACUTE INCLUSION-BODY ENCEPHALITIS: A POSSIBLE ASSOCIATION WITH INFECTIVE HEPATITIS *

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SINCE Dawson reported two cases of an unusual subacute progressive encephalitis in 1933 and 1934, there has been increasing recognition of a disorder characteristically affecting children in which many cortical neurones and glial cells have type-A intranuclear inclusions. In 1945 van Bogaert described three similar cases under the title of subacute sclerosing leucoencephalitis. It is now recognised that these are essentially the same disorder. Intranuclear inclusions are more easily found in cases which die after a short course, the more chronic ones showing more demyelination and sclerosis of the white matter.

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Many case-reports in the next ten years made the clinical picture familiar. There is a gradual onset of mental deterioration in a child or adolescent, followed by night terrors or hallucinations, and then a stage characterised by periodic involuntary movements at regular intervals of 5–10 seconds. In this stage the electroencephalograph shows a typical picture of periodic high-voltage complexes of stereotyped pattern. A terminal stage of akinetic mutism leads to inevitable death. The total duration is usually about 2 years though survival for 8 years is possible. Remissions are possible in the early stages. Sooner or later the C.S.F. colloidal-gold curve is of paretic type. The disorder is certainly not so rare as the number of papers would suggest. Further clinical description is superfluous but research must be concentrated on discovering the cause of this strange illness, presumed to be caused by a virus though inclusion-bodies may have a biochemical origin.

This paper is based on a study of nine typical cases seen in Edinburgh in the past ten years (four studied in detail by Dr. J. B. Stanton and myself). Dr. E. A. Carmichael kindly allowed me to study the records of a case under his care (case 5). A further case is reported which was diagnosed as subacute inclusion-body encephalitis but which subsequently made a complete recovery (see table, case 11).

The first ten cases tabulated were typical in all respects except that case 2 is still alive 8 years from the onset and has not yet had a paretic type of Lange curve in her cerebrospinal fluid. The unusual circumstances of cases 1, 2, and 3 being in the ward at the same time drew my attention to the coincidence that each had a previous history of jaundice. Scrutiny of the records of the other Edinburgh cases showed no recorded history of jaundice but case 4 was noted to have spider nævi on the skin and the serum icteric index was 14 (upper limit of normal 5–7). Liver function tests were otherwise normal. Case 5 had no history of jaundice but the plasma thymol turbidity test gave 8 units, and there was a 4+ colloidal gold reaction.

Material obtained by liver biopsy from cases 1 and 3 was studied, with blood and C.S.F., by the University department of virology without positive findings. The postmortem appearance of the liver in these cases, in common with the others studied by necropsy, was normal. This merely reminds one that previous infective hepatitis is not excluded by normal histological findings in the liver at death.

Case 11 had jaundice at the age of 11. 16 months later she became listless, lost her appetite, and began to do poorly at school. After 3 months like this she had a focal seizure. She was admitted to the department of surgical Neurology (Prof. N. M. Dott) with doubtful spastic signs on the right side. She was afraid, and very restless. An E.E.G. (unfortunately no longer available) showed widespread delta activity with greater amplitude in the right central region. The C.S.F. contained 22 lymphocytes per c.mm., 50 mg. protein per 100 ml., Lange 1113330000. In the next few days the cells increased to 32 per c.mm., protein to 100 mg. per 100 ml. and the Lange curve became 4555532100. The Wassermann reaction was negative. She was transferred to the neurological unit (Dr. E. Levin) with a diagnosis of Dawson-type encephalitis. All clinical and C.S.F. signs gradually returned to normal in 4 months. When I saw her recently she was perfectly well and had a normal E.E.G. By current criteria is must be considered that the diagnosis was wrong and this case is placed in a separate category.

FINDINGS IN THE ELEVEN CASES

Case no.	1	2	3	4	5	6	7	8	9	10	11
Sex	F	F	M	M	F	M	M	M	M	F	F
Age at onset (yr.) ..	14	11	11	12	8	7	7	14	11	7	12
Jaundice	5 yr.	weeks	8 yr.	..	..	..	..	..	..	..	1 yr.
Spider nævi ..	+	?	+	+	..	..	..	..	..	..	+
Liver function tests	Normal	Normal	Normal	?*	Abnormal	..	..	..	..	..	No record
C.S.F. Lange curve	Paretic	Normal	Paretic	Paretic	Paretic	Paretic	Paretic	Paretic	Paretic	Paretic	Paretic
E.E.G.	R.C.	R.C.	R.C.	R.C.	R.C.	R.C.	R.C.	..	R.C.	R.C.	Diffuse delta
Inclusion bodies ..	+	..	+	No necropsy	+	No necropsy	−ve biopsy only	+	−ve (necropsy)	−ve biopsy only	Recovered

R.C. = typical rhythmical complexes. * = raised serum icteric index only.

In the remaining ten cases there are three with a definite history of infective hepatitis and another two with abnormalities suggesting previous liver disease—a minimum of 30%, with a possible 50% of the definite cases of subacute leucoencephalitis of Dawson/van Bogaert type. Through the kindness of the Edinburgh Education Department I have been able to question 20,000 secondary-school children in the age-group 12–18. 840 of these gave a history of jaundice. For the present purpose all positive statements were accepted although neonatal jaundice and non-icteric cases were known to be included. Despite recent epidemics, the total incidence of jaundice in the previous medical histories of these children was under 5%. The probability of finding three cases (possibly five) in a sample of ten children from the same age-group and environment is about 1 in 1000 ($P < 0.001$).

Discussion

Jaundice shortly before the onset of subacute sclerosing leucoencephalitis was reported by Thiry (1956) and by Brucher and Dechef (1957). Bickerstaff (personal communication) had a case of subacute inclusion-body encephalitis aged 7 who had had jaundice at the age of 3 years. Thiry (1956) found liver enlargement in another case. Martin and Isler (1957) noted gastrointestinal upset at the onset of encephalitic symptoms.

It is evident that clinical jaundice is a rare precursor of subacute inclusion-body encephalitis, but in one of the first reports Dawson (1934) considered the possibility of an association because of the similarity of the inclusion-bodies to those described by Lucksch (1923) in the substantia nigra of the brain from a patient who had died of hepatic cirrhosis. Lucksch found similar inclusions in the brains of patients who had other diseases and it should be remembered that his survey followed the epidemic period of encephalitis lethargica. Lucké (1944) found perivascular round-cell infiltration in the basal ganglia and other parts of the brain in fatal cases of hepatitis. His findings were confirmed by Stokes et al. (1945) in their review of the neurological complications of infective hepatitis. They were concerned with the acute stage of the illness and the encephalopathies described bear no resemblance to the Dawson/van Bogaert type of subacute encephalitis.

Jaundice, hepatomegaly, or gastrointestinal disorder of subicteric type has been associated with Schilder's disease (Kaltenbach 1922, Meyer and Tennent 1936), acute necrotising encephalitis with inclusions (Radermecker 1956, Recordier et al. 1956) and with a progressive subacute encephalopathy reported by Pallis and Spillane (1957) with certain clinical resemblances to the van Bogaert type of encephalitis. The exact nosological position of these disorders is debatable and the case-reports do not suggest that they should be included with the Dawson/van Bogaert disorder, but it may be well to remember that the assumption of a virus encephalitis in the latter is not firmly based. Inclusion-bodies may also have a biochemical origin. Confirmation of the suggested association between hepatitis and encephalitis would add weight to the virus hypothesis.

It is well known that many specific viruses may cause either hepatitis or encephalitis. Familiar examples are yellow fever, herpes-simplex infection (France and Wilmers 1953, Brain 1956), cytomegalic inclusion disease of infants, infectious mononucleosis, and "benign myalgic encephalomyelitis". Some of these viruses have been considered by previous workers, and a protozoal infection, such as toxoplasmosis, has also been sought for in vain. One of Dawson's cases had herpes febrilis and he and later workers discussed the possibility that the herpes virus also caused inclusion-body encephalitis of the type under discussion, but there is no doubt that herpetic encephalitis and cytomegalic inclusion disease, the only likely candidates in the above list, can be excluded on histological grounds. Complement-fixation tests with herpes simplex antigen have been negative in the sera of most cases of subacute encephalitis (Greenfield 1958). All writers report completely negative results of virus studies on blood, C.S.F., or brain tissue from cases of subacute encephalitis. Is it possible that the unidentified virus of infective hepatitis is responsible? There is a strong suspicion that it lingers in an active state in the liver for many years (Cullinan et al. 1958). It is possible that it might rarely cause subacute encephalitis in young people if the brain is later damaged by head injury or some trivial infection. Case reports often mention head injuries or a zymotic disease as an immediate precursor. Greenfield writes: "There are a number of viruses which may produce encephalitis in laboratory animals, but in man have only been known to cause hepatitis or more general disease without symptoms of encephalitis. It is possible that a virus of this kind may attack the central nervous system in an occasional human case as is now known to happen with the common virus of herpes simplex". The available evidence is inconclusive but it is reported in support of the virus hypothesis of subacute inclusion-body encephalitis and to alert other workers to the possibility that it might be related to infective hepatitis. Retrospective diagnosis by examination of the liver at necropsy is unreliable evidence of freedom from infection since it is shown here that the liver was completely normal in two cases although there were unequivocal histories of previous jaundice.

Thiry (1956) and Brucher and Dechef (1957) considered that the preceding jaundice which occurred in their cases indicates a hepatic stage in the invasion of the body by a virus causing subacute encephalitis. If the association of jaundice with encephalitis after a long latent period, which is the point I want to emphasise, is confirmed, the interpretation is rather different. The virus of infective hepatitis, which has defied isolation and identification so far, with its known predilection for childhood subicteric infection, and its frequent tendency to remain in the body as a potential pathogen would be a suitable candidate for the causative agent of subacute inclusion-body encephalitis. Confirmation must wait for advances in virological technique. In the meantime it is hoped that this tentative report will prompt inquiry for a previous history of jaundice.

Summary

Ten cases of subacute encephalitis of Dawson/van Bogaert type are reported. Five patients showed evidence of previous liver disease, three having had clinical hepatitis. A case of subacute encephalitis of similar onset 16 months after jaundice resolved completely in 7 months. Reported cases of subacute sclerosing leucoencephalitis and other subacute encephalopathies preceded by jaundice are reviewed. Subacute inclusion-body encephalitis may be a rare manifestation of infection by a virus which usually causes infective hepatitis.

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REFERENCES

Bogaert, L. van (1954) *J. Neurol. Neurosurg. Psychiat.* **8**, 101.
Brain, R. T. (1956) *Brit. med. J.* **1**, 1061.
Brucher, J. M., Dechef, G. (1957) *Acta Neurol. Psychiat. Belg.* **10**, 775.
Cullinan, E. R., King, R. C., Rivers, J. S. (1958) *Brit. med. J.* i, 1315.
Dawson, J. R. (1933) *Amer. J. Path.* **9**, 7.
— (1934) *Arch. Neurol. Psychiat. Chicago*, **31**, 685.
France, N. E., Wilmers, M. J. (1953) *Lancet*, i, 1181.
Greenfield, J. G. (1958) Neuropathology. London.
Kaltenbach, H. (1922) *Z. Psychiat. Neurol.* **75**, 138.
Lucké, B. (1944) *Amer. J. Path.* **20**, 471.
Lucksch, F. (1923) *Beitr. path. Anat. alg. Path.* **71**, 201.
Martin, F., Isler, W. (1957) *Arch. Suisses. Neurol. Psychiat.* **79**, 73.
Meyer, A., Tennent, T. (1936) *Brian*, **59**, 100.
Pallis, C. A., Spillane, J. D. (1957) *Quart. J. Med.* **26**, 349.
Radermecker, J. (1956) *Rev. neurol.* **95**, 580.
Recordier, M., Gastaut, H., Bogaert, L. van, Radermecker, J. (1956) *Rev. neurol.* **95**, 116.
Stokes, J. F., Owen, J. R., Holmes, E. G. (1945) *Brit. med. J.* ii, 642.
Thiry, S. (1956) *Rev. med. Liege*, **11**, 225.

THYROIDECTOMY UNDER HYPOTHERMIA IN A PREGNANT PATIENT WITH THYROID CRISIS

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WITH the introduction of the anti-thyroid drugs and the routine preoperative use of iodine, thyroid crisis has become very rare indeed.

McArthur et al. (1947) recorded 36 crises in a series of 2033 hyperthyroid patients seen over twenty-five years. Hansen et al. (1957) reported 4 postoperative crises in 608 thyroidectomies performed from 1941 to 1950. Beahrs et al. (1956) mentioned 2 deaths from thyroid crisis in a series of 14,374 thyroidectomies; these had occurred in 1943 and 1944. Lamberg (1959) emphasised the difficulty of distinguishing severe thyrotoxicosis from impending or manifest crisis, and cited McArthur's definition of crisis as a "life-endangering exacerbation of thyrotoxicosis" (McArthur et al. 1947). He described 17 cases of impending or actual storms observed in the years 1955–58. Waldstein et al. (1960) have reviewed their experience with 21 episodes of thyroid storm occurring between 1955 and 1958. They stress the undesirability of surgery and advocate intravenous iodide, anti-thyroid drugs, reserpine, and hydrocortisone.

The infrequency of thyroid crisis makes it difficult to assess the influence of modern remedies. Recently we had the problem of handling a young woman with severe thyroid crisis. Medical treatment was of no avail, and, since her condition was deteriorating rapidly, it was decided to submit her to thyroidectomy. This was performed under hypothermia, which was maintained for over ninety-six hours.

The use of hypothermia in the management of postoperative thyroid crisis has been described, but we have not encountered a report of "emergency thyroidectomy" performed in this manner. We believe that the procedure was life-saving in our patient, and report our experience in the hope that others may confirm its usefulness.

Case-record

A Coloured woman, aged 27, had apparently first fallen ill in April, 1959, when she was referred to Groote Schuur Hospital owing to alteration in personality. She had become depressed, listless, and uninterested. Physical examination revealed tachycardia but no other signs of hyperthyroidism, and the thyroid gland was said to be impalpable. A psychiatric opinion was obtained and "schizo-affective disorder of depressive type" was diagnosed and electroconvulsive therapy was instituted. Initially mood improved, but regression was apparent and physical examination in July, 1959, suggested hyperthyroidism. Salient features included a palpable thyroid swelling, hot extremities, and a fine tremor. The pulse-rate was 132 per minute. ^{131}I-uptake studies showed rates of 84% and 80% at six and twenty-four hours respectively. After 120 μg. of triiodothyronine daily for six days, the six-hour uptake was 93%. The patient failed to return for a twenty-four-hour uptake study.

Apart from one reattendance at the psychiatry outpatient department on Oct. 27, 1959, when she was stated to be much better, the patient failed to report to hospital. No anti-thyroid treatment had been instituted.

In March, 1960, she reappeared and was referred to the endocrine clinic, where severe hyperthyroidism was evident and the patient was admitted to hospital. She was anxious, restless and tremulous, sweating, and hot. The pulse-rate was 132 per minute and there was now a large diffuse goitre. There were no eye signs of hyperthyroidism. She averred that she had gained 30 lb. in weight in the past few months; her appetite had been ravenous. Treatment was started with carbimazole ('Neomercazole') 20 mg. t.d.s., thyroxine 0·1 mg. b.d., and phenobarbitone gr. $^1/_2$ t.d.s. Ten days later the patient was discharged in an apparently improving condition.

On April 5, 1960, she was readmitted with fever, sore throat, and cough. The temperature was 100°F on admission, and the tonsils were acutely inflamed. The white-blood-cell count was 16,300 per c. mm. (polymorphs 80%). Erythromycin was administered for a week. The temperature subsided, and she was discharged comparatively well on April 14, 1960. Tachycardia of 110 per minute was present on discharge.

Carbimazole and thyroxine were continued, and return visits showed gradual but definite improvement. On June 13, 1960, the patient was considered well enough to change to Lugol's iodine, which was given in a dosage of 10 minims t.d.s. until July 4, 1960, when she was admitted for thyroidectomy.

On admission she was still thyrotoxic. Pulse-rates ranged from 118 to 140 per minute, and there was much cardiac

activity with an obvious high-output state. The thyroid gland had enlarged immensely and was very firm. In view of the persistent hyperthyroidism, operation was deferred. Iodine was stopped and administration of carbimazole was reinstituted.

At the beginning of August, 1960, diarrhœa and vomiting developed. This was not controlled by sulphathalidine given by her general practitioner, and the patient's condition gradually deteriorated until she was readmitted on Aug. 9 with the diagnosis of impending thyroid storm. She was now about three months pregnant.

Carbimazole was continued and erythromycin was again instituted because of an obvious recrudescence of acute tonsillitis. Owing to severe restlessness and excitability an attempt was made to induce hibernation by administering chlorpromazine and amylobarbitone sodium alternately in large doses. Some improvement resulted initially; but the pyrexia persisted, the pulse-rate rose to 172 per minute, the patient began to sweat profusely, and clouding of consciousness supervened. Bronchopneumonia was diagnosed, and chloramphenicol 500 mg. six-hourly was started on Aug. 26. In addition, intravenous hydrocortisone and iodine were administered. In view of her grave condition, emergency thyroidectomy was decided upon on the same afternoon.

Thyroidectomy

Hypothermia was induced, under heavy preoperative sedation, by a cooling blanket. Nitrous oxide 70% and oxygen 30% were administered endotracheally with spontaneous respiration. The temperature was monitored by an œsophageal electrode. Over a period of a hundred and thirty minutes it dropped from 100°F to 88°F, while the systolic blood-pressure fell from 180 to 120 mm. Hg and the pulse-rate from 150 to 90 per minute.

The selected target temperature was 90°F, which, it was hoped, would afford considerable reduction in metabolic rate without undue risk of cardiac arrhythmia, to which this patient was especially prone. No arrhythmia was observed, and the temperature was soon stabilised at 90–91°F.

A standard subtotal thyroidectomy was performed without further anæsthetic difficulties. At the end of the operation a tracheotomy was done to facilitate removal of the copious pulmonary secretions and to ensure a patent airway during the proposed prolonged hypothermia.

Postoperative Management

On the patient's return to the ward hypothermia was continued, rectal temperatures being maintained at 90–92°F. The pulse-rate fluctuated between 100 and 120 per minute. To control shivering a mixture of promethazine hydrochloride 50 mg., pethidine 50 mg., and chlorpromazine 50 mg. was made up to 20 ml. 2–4 ml. of this mixture was administered intravenously as required. During the first postoperative night she received 40 ml. In addition 5% dextrose-water with 300 mg. hydrocortisone and 30 minims Lugol's iodine were administered intravenously during the night. This regimen was continued during the next twenty-four hours. Thereafter, no further iodine was given; hydrocortisone was gradually reduced and finally stopped on Aug. 31.

On Aug. 29 an attempt was made to restore her body-temperature to normal. The pulse-rate, which had been maintained at an average of 120 per minute, immediately rose to 160 per minute. Hypothermia was therefore reinstituted, with prompt lowering of the pulse-rate. A stomach-tube was passed for purposes of feeding. Shivering was prevented by the use of amylobarbitone sodium, pethidine and promethazine hydrochloride.

On Aug. 30 respiratory difficulty became severe. Bronchoscopy was performed and a thick plug of mucus was aspirated. Later in the day the decision was taken to stop the hypothermic measures, since it was feared that the depression of coughing might aggravate the pulmonary infection. Sedation was continued until the patient was normothermic, thus obviating the violent bouts of shivering that had accompanied the previous attempt at stopping hypothermia. Her pulse-rate rose to about 150 per minute.

The antibiotic was changed to kanamycin 500 mg. six-hourly, and mystatin 500 mg. twice daily was added to prevent fungal complications.

On Aug. 31 the temperature rose to 105°F. Cooling was achieved by means of fans placed over buckets of iced water. The temperature subsided to 99°5F. Further bronchoscopic aspiration produced thick plugs of mucus.

From this time gradual but definite improvement resulted. Sedation was stopped on Sept. 1, and the pulse-rate gradually slowed over the next few days to a level of 100-110 per minute. An additional complication during this phase was the development of frank hæmaturia followed by temporary oliguria. This was attributed to kanamycin, which was changed to a combination of erythromycin 500 mg. six-hourly with novobiocin 500 mg. six-hourly.

The final episode was the onset of vaginal bleeding on Sept. 4 which culminated in the evacuation of a dead 4-month fœtus on Sept. 11. Within a matter of hours her pulse-rate dropped to 70–80 per minute.

Recovery continued, and the patient was discharged from hospital on Sept. 17 quite well.

Discussion

Thyroid crisis of this severity is rarely seen today. In retrospect it seems clear that the change to iodine preoperatively was premature, as the patient was not properly controlled by anti-thyroid agents at the time. The major precipitating cause of her crisis seems to have been the withdrawal of iodine, since rapid and severe deterioration followed. McArthur et al. (1947) regarded iodine withdrawal as the commonest precipitating factor in "medical" storms, and reported 4 cases in which this was a factor. In 2 of these patients there was subsequent difficulty in management with a lack of the usual responsiveness to propylthiouracil. We encountered the same refractoriness in our patient. Lamberg (1959) stresses the importance of chronicity of the disease as a factor in the development of thyroid crisis. The delay in diagnosis of the present case may be significant.

Two other factors may have contributed to the severity of this patient's illness. The first was the presence of recurrent acute tonsillitis which culminated in bronchopneumonia. Upper-respiratory-tract infections are notoriously associated with thyroid storm, and indeed their manifestations often form an intrinsic part of the clinical picture. Another factor appears to have been the pregnancy. This was not diagnosed until the patient's final admission, her amenorrhœa previously being attributed to her constitutional ill-health. The drop in pulse-rate after evacuation of the uterus was dramatic and suggests that the presence of a fœtus played some part in the persistence of tachycardia.

In retrospect certain points of management stand out. Probably over-enthusiastic sedation contributed to the development of bronchopneumonia, which in turn aggravated the hyperthyroidism. Extreme restlessness and confusion, however, required control and it was hoped that the metabolic rate might be lowered by means of sedation. Successful treatment of thyroid crisis by hibernation induced in this manner has been recorded (Terracol and Camps 1958).

The immediate effect of hypothermia on the pulse-rate was striking and maintained. We were uncertain how long postoperative hypothermia should be continued. A tentative raising of the patient's body-temperature on Aug. 29 was attended by a prompt increase in tachycardia. On the following day the decision was taken to terminate hypo-

thermia on account of difficulty experienced in maintaining a clear airway in the absence of cough. Again the pulse-rate rose. If it had been possible, we would have preferred to maintain the hypothermia longer on the premise that a large pool of thyroxine might still be circulating since its rate of degradation is probably slowed under hypothermia.

Summary

A case is described in which emergency thyroidectomy was undertaken because of uncontrolled hyperthyroidism. The operation was performed under hypothermia, which was maintained for over ninety-six hours. This procedure is believed to have been life-saving.

We wish to thank Dr. J. G. Burger, superintendent of Groote Schuur Hospital, for permission to publish this report; and Prof. F. Forman and Dr. W. P. U. Jackson for helpful criticism of the manuscript. In particular, our thanks must go to the house-surgeons and nursing staff, whose zealous efforts played such a large part in the successful treatment described here.

REFERENCES

Beahrs, O. H., Ryan, R. F., White, R. A. (1956) *J. clin. Endocrin.* **16**, 1456.
Hansen, T. S., Friis, Th., Fuchs, F., Iverson, K. (1957) *Danish med. Bull.* **4**, 1.
Lamberg, B-A. (1959) *Acta med. scand.* **164**, 479.
McArthur, J. W., Rawson, R. W., Means, J. H., Cope, O. (1947) *J. Amer. med. Ass.* **134**, 868.
Terracol, J., Camps, F. (1958) *Rev. Laryng., Bord.* **79**, 1092.
Waldstein, S. S., Slodki, J. J., Kaganiec, G. I., Bronsky, D. (1960) *Ann. intern med.* **52**, 626.

Preliminary Communications

INTRAVENOUS REPLACEMENT OF HUMAN SPLENIC TISSUE

TREATMENT of cancer by wide-field irradiation or the administration of cytotoxic drugs may result in severe bone-marrow aplasia, and it is becoming commonplace to overcome this by removing bone-marrow before the course of treatment and replacing it afterwards by intravenous infusion (for review see Woodruff [1 2]).

This is certainly a valuable procedure, but the indications for it are limited because of the frequency with which many tumours metastasise to bone. Moreover, transplantation of marrow does relatively little to hasten the regeneration of lymphoid tissue, which is also readily damaged by ionising radiation and cytotoxic drugs, and which plays an important role not only in the defence of the body against infection, but also, we believe, in limiting the spread of cancer.

It occurred to us, therefore, to study the effect of removing the spleen, which is but rarely the site of metastasis, from patients with advanced cancer, prior to irradiation or chemotherapy, and replacing it later intravenously in the form of a cell suspension. Such a suspension, it was felt, would contain a large number of lymphocytes and cells destined to become lymphocytes, and perhaps also enough undifferentiated stem-cells to initiate the formation of red blood-cells, granulocytes, and blood-platelets.

It was decided to use splenic tissue alone when dealing with tumours which commonly metastasise to bone, or in any case when there was cytological or radiological evidence of marrow involvement, but in other cases to combine replacement of bone-marrow and splenic tissue.

Our first patient was treated in March, 1960, and has already been reported.[2] She was suffering from very advanced neoplastic disease, and did not live long enough for the value of the procedure to be assessed, but it was at least established that the intravenous injection of $2{\cdot}2 \times 10^9$ nucleated cells from the patient's own spleen was well tolerated. We have now two more cases to report.

1. Woodruff, M. F. A. The Transplantation of Tissues and Organs; chap. 22. Springfield, Ill., 1960.
2. Woodruff, M. F. A. *J. R. Coll. Surg. Edinb.* 1961, **6**, 75.

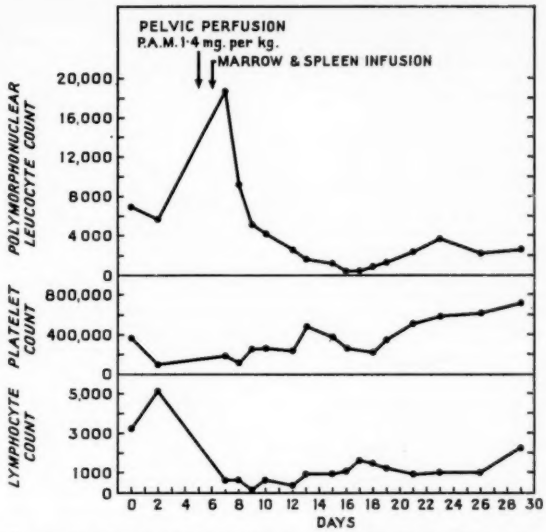

Fig. 1—Graph of peripheral blood-counts of polymorphonuclear leucocytes, lymphocytes, and platelets in case 1.

TWO FURTHER CASES

CASE 1.—Mrs. A., aged 47, weighing 54 kg., had had a malignant melanoma removed from her right leg in April, 1960, combined with an extensive dissection of the inguinal and iliac nodes, all of which were found to contain at least microscopic metastases. When she was admitted to the Edinburgh Royal Infirmary in January, 1961, there were numerous subcutaneous melanotic nodules in the right thigh, a palpable node $1{\cdot}5 \times 1{\cdot}0$ cm. in the groin, and a subcutaneous swelling 2 cm. in diameter near the umbilicus.

Under general anæsthesia bone-marrow was aspirated from both iliac crests, the patient's spleen was removed, and perfusion of the pelvis and right lower limb was carried out using 75 mg. phenylalanine mustard. At the same time the nodule near the umbilicus was excised, and found to be melanomatous. It seemed likely that there would be tumour cells beyond the limits of the perfusion, and for this reason a fairly large leak of drug into the systemic circulation was deliberately accepted.

Cell suspensions were prepared from the spleen and marrow by the technique described previously,[2] and kept at 4°C. No neoplastic cells could be demonstrated in the marrow, and 18 hours after the perfusion the whole of the marrow suspension, containing $2{\cdot}6 \times 10^9$ nucleated cells, was given to the patient by intravenous infusion. An hour later the splenic suspension, containing 30×10^9 nucleated cells, was administered in the same way. The patient's temperature rose to 103°F but subsided next day. There was a rapid fall in the lymphocyte-count which reached a minimum of 200 per c.mm. after 4 days, while the polymorphs rose to 18,000 per c.mm. and then gradually fell, reaching a minimum of 400 per c.mm. 10 days after the perfusion. There was no significant fall in the blood-platelets.

The subsequent recovery is illustrated in fig. 1. The tumours regressed temporarily, but 2 months after perfusion several new ones had appeared, and many more have developed since though the patient's general condition is still fairly good.

CASE 2.—Mrs. B., aged 63, weighing 67 kg., was admitted in February, 1961, on account of a recurrent malignant synovioma of the right groin, which had been treated previously by surgical excision and radiotherapy. A chest X-ray showed a small

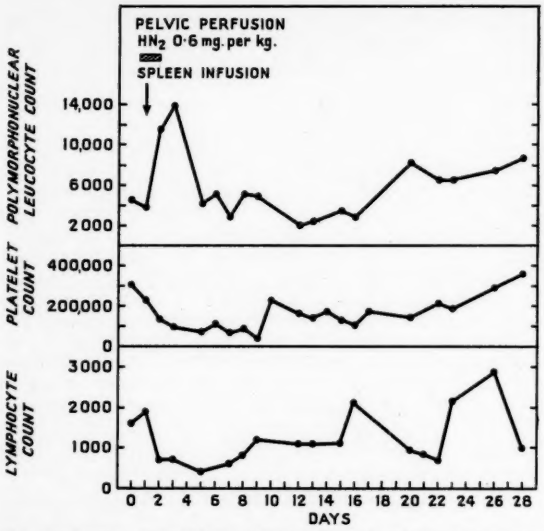

Fig. 2—Graph of peripheral blood-counts of polymorphonuclear leucocytes, lymphocytes and platelets in case 2. Note the satisfactory maintenance of the lymphocyte-count.

opacity in the second left interspace, and another in the first right interspace, which it was felt might be metastases.

Under general anæsthesia the spleen was removed and perfusion of the pelvis and upper part of the right thigh was carried out using 42 mg. nitrogen mustard. Monitoring with ^{131}I serum-albumin showed that there was a large leak into the general circulation; so a cell suspension containing 20×10^9 nucleated cells was prepared from the spleen (which had been kept at 4°C) and given by intravenous infusion, starting 6 hours after completion of the perfusion. The patient was nauseated for a few days but showed no symptoms attributable to the infusion.

The subsequent blood changes are shown in fig. 2, from which it will be seen that there was a sharp fall in lymphocytes which recovered very quickly, the usual increase in polymorphs followed by a moderate fall and subsequent recovery, and a moderate fall in blood-platelets. The tumour regressed satisfactorily and has not recurred, while the opacities in the lungs have remained unchanged. The left leg became swollen after the perfusion, probably through deep-vein thrombosis, but the swelling has been satisfactorily controlled with an elastic stocking.

COMMENT

These cases confirm that intravenous infusion of autologous spleen cells is safe, and suggest that it may help to promote hæmopoietic recovery as judged by the peripheral blood-count.

It should be possible, by a sufficiently extensive and properly controlled clinical trial, to determine whether the procedure contributes to the destruction of the tumour; but this may require more cases than we can possibly handle, and we give this preliminary report in the hope of encouraging similar investigations in other hospitals. In addition the problem is being investigated in laboratory animals.

It would be of great interest to study the subsequent life-history of the infused cells; but, as these are autologous, neither they nor their descendants can be recognised unless a label can be attached which is capable of persisting through several cell divisions. So far we have not succeeded in solving this problem.

We have refrained from using homologous spleen-cells, and would advise others to refrain also, because of the risk of secondary disease.[1] There is evidence that this can occur in irradiated humans after infusion of homologous bone-marrow,[3] and it seems virtually certain, from experiments in animals and also on theoretical grounds, that spleen would be very much more dangerous than marrow.

This work was supported by a grant from the British Empire Cancer Campaign, which we gratefully acknowledge. We are indebted to Prof. Alexander Haddow, F.R.S., for providing the phenylalamine mustard used in the first of the two cases, and to several of our colleagues who have helped to prepare the cell suspensions. We should also like to thank Mr. J. Gardner Jamieson, F.R.C.S., and Mr. J. P. Turney, F.R.C.S., for referring the cases to us.

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FOREARM METABOLISM IN OBESITY AND ITS RESPONSE TO INTRA-ARTERIAL INSULIN

EVIDENCE FOR ADAPTIVE HYPERINSULINISM

OBESITY is considered ordinarily to be a consequence of overeating by an otherwise normal person, but the notion persists that there may be some underlying metabolic defect. The man of 70 kg., on becoming 20% overweight, doubles his adipose organ mass.[4] If obesity is viewed as a state of chronic substrate excess necessitating increase in fat storage of this magnitude, one might indeed predict that certain metabolic adjustments would occur, resulting in alterations in, but not implying a primary disturbance of, intermediary metabolism.

We have examined metabolism of obese subjects by measuring metabolic events in the forearm, which is predominantly skeletal muscle and adipose tissue, to determine what departures from normal take place and what light these differences may shed on adaptation to chronic substrate excess.

METHODS

Six young subjects, four males and two females, were studied, all approximately 20% overweight but otherwise healthy; all had been actively gaining weight in the six to twelve months preceding the test and in none was there a family history of diabetes. Subjects were given a 200 g. carbohydrate diet for the three days before the test. No food was permitted after 8 P.M. the previous night. The test was performed between 9 A.M. and 1 P.M., that is 13–17 hours after the last meal.

A brachial artery, an ipsilateral antecubital vein draining mostly muscle, and a superficial vein draining mostly forearm adipose tissue and skin were cannulated by techniques described previously.[5] Blood-flow was measured by the indicator-dilution method, based on continuous injection at constant rate of the dye T–1824. Circulation to the wrist and hand was excluded during experimental periods by a sphygmomanometer cuff inflated to at least 100 mm. Hg beyond systolic pressure.

Uptake or production of a metabolite is given by the equation $\dot{Q} = F(A-V)$ where F is blood or plasma flow per minute per 100 ml. of forearm, A is concentration of metabolite in arterial blood or plasma and V is its concentration in deep venous blood. This overestimates muscle metabolism in that it assigns all forearm blood-flow to muscle. The errors have been discussed elsewhere.[5] We are unable to estimate either blood-flow through adipose tissue or the mass of adipose tissue, but useful

3. Mathé, G., Bernard, J., Vries, J. de, Schwarzenberg, L., Larrieu, M. J., Lalanne, C. M., Dutreix, A., Amiel, J. L., Surmont, T. *Rev. Hémat.* 1960, **15**, 115.
4. Keys, A., Brozek, J. *Physiol. Rev.* 1953, **33**, 245.
5. Andres, R., Cader, G., Zierler, K. L. *J. clin. Invest.* 1956, **35**, 671.

information is still obtained by comparing arterial and superficial venous concentration differences of several metabolites.

In an effort to shed further light on previous observations that obese subjects show resistance to the hypoglycæmic effects of insulin administered intravenously [6–8] we have examined the response of the forearm of obese subjects to a dose of intra-arterial insulin standardised previously in normal subjects.[9] Our technique lends itself nicely to examination of local effects of hormones. The hormone is added to the solution containing blue dye, T–1824, injected at constant rate in amounts so small that their arrival into the general circulation stimulates no measurable response. Thus one observes as far as possible only the effects of the hormone on forearm tissues; the response is not, as in the case of the more conventional intravenous insulin tolerance tests, complicated by counter-regulatory measures the body may institute.

Glucagon-free insulin was injected, along with blue dye, into the brachial artery in a dose of 100 μunits per kg. body-weight per minute for 26 minutes. When this dose is diluted by brachial arterial plasma flowing by the injection site, the concentration of insulin in forearm arterial plasma is approximately 300 μunits per ml. Circulation to the wrist and hand was excluded during the full period of insulin administration. Blood samples were drawn 12, 18, and 26 minutes from commencement of the insulin infusion and for periods up to one hour thereafter.

RESULTS AND DISCUSSION

Rates of Uptake or Production

Values for basal rates of uptake of glucose, of O_2, and of potassium, and rates of production of CO_2 and of lactate $(\dot{Q}_G, \dot{Q}_{O_2}, \dot{Q}_K, \dot{Q}_{CO_2}$, and $\dot{Q}_L$ respectively), expressed as the mean for the six obese subjects studied, appear in table I

TABLE I—OBSERVATIONS ON BASAL FOREARM MUSCLE METABOLISM IN CONTROL AND OBESE SUBJECTS

—	Controls • (μM per min. per 100 ml. forearm)	Obese (μM per min. per 100 ml. forearm)	P
Potassium	−0·43 ± 0·076	+0·02 ± 0·058	<0·001
Glucose	0·52 ± 0·075	0·72 ± 0·132	<0·05
O_2	11·6 ± 0·97	11·0 ± 1·43	N.S.
CO_2	8·7 ± 0·94	6·9 ± 1·03	N.S.
Respiratory quotient	0·76 ± 0·02	0·70 ± 0·045	N.S.
L/G ratio†	42·3 ± 8·3%	24·3 ± 6·7%	<0·05

Data are means ± standard errors of mean. P is probability that differences between mean in control and in obese group might occur by chance, estimated by *t* test. N.S., meaning not significant, is applied to P > 0·05.
• See reference 5.
† L/G = 100 (1/2 lactate-arteriovenous-difference/glucose-arteriovenous-difference). Since production of 2 moles of lactate implies dissimilation of 1 mole of glucose, this ratio yields the percentage of glucose uptake accounted for by lactate production.

along with control values which represent mean values of more than 60 experiments.

Potassium uptake.—Net movement of potassium out of resting muscle into plasma, characteristic in control subjects under the conditions of these experiments,[10] was absent in these obese subjects, in whom there was no net movement of potassium.

Glucose uptake.—Mean glucose uptake of 0·72 μM per minute per 100 ml. forearm represents a value 40% greater than that of controls.

O_2 uptake, CO_2 production and respiratory quotient.—No differences from controls are apparent in O_2 consumption or CO_2 production by forearm muscle in obese subjects. The respiratory quotient of 0·7, as in normal muscle, is compatible with lipid oxidation and provides strong indirect evidence that there is no quantitative defect in lipid oxidation.

Lactate production by forearm muscle in obese subjects does not differ quantitatively from that of controls.

The probable metabolic fate of glucose.—The L/G ratio, which, as explained in the legend to table I, defines the percentage of glucose uptake accounted for by lactate production, is significantly lower in forearm muscle of obese subjects (24·3%) than in controls (42·3%).

TABLE II—MEAN EFFECT OF INSULIN ON FOREARM METABOLISM IN CONTROL AND OBESE SUBJECTS

Minutes after insulin started	Glucose uptake (μM per min. per 100 ml. forearm)		Change in potassium movement (μM per min. per 100 ml. forearm)	
	Controls •	Obese	Controls •	Obese
0	0·52 ± 0·075	0·72 ± 0·132	0	0
12	2·7 ± 0·811	1·0 ± 0·25	0·62 ± 0·292	0·21 ± 0·043
18	4·71 ± 1·026	1·37 ± 0·412	1·06 ± 0·367	0·21 ± 0·098
26	6·78 ± 1·25	2·21 ± 0·423	1·24 ± 0·355	0·52 ± 0·177
40	6·07 ± 0·998	1·94 ± 0·568	1·47 ± 0·375	0·49 ± 0·178
60	3·52 ± 0·645	1·09 ± 0·547	1·30 ± 0·294	0·5 ± 0·17

Data are means ± standard errors of mean. Insulin administered intra-arterially for 26 minutes beginning at time zero. Values for glucose uptake given at time zero are means of control measurements taken before insulin infusion started. Because of wide differences between control and obese subjects in basal potassium uptake (see text), effects of insulin administration are expressed as the increase in net inward movement of potassium compared to potassium movement at time zero.
• See reference 9.

Forearm muscle of obese subjects takes up more glucose than controls. Since this occurs with neither increase in O_2 consumption nor rise in respiratory quotient, it is probable that the glucose which is taken up in excess of that abstracted by controls is not combusted but stored presumably largely as muscle glycogen.

Evidence for Endogenous Hyperinsulinism

Previous studies from this laboratory [9] have demonstrated that insulin, infused into the brachial artery of control subjects, reverses net potassium efflux and increases glucose uptake by forearm muscle. Only a minor fraction of the glucose is accounted for by lactate production and none is oxidised to CO_2. The respiratory quotient of forearm muscle does not rise. Metabolic events in the forearm of obese subjects in the absence of exogenous insulin resemble those in the normal forearm exposed to insulin and suggest that in obesity there is hyperinsulinism, presumably adaptive to unusual quantities of substrate. This may be one of many functional changes in endocrine status facilitating storage of fat and carbohydrate.

This hypothesis was advanced by Brobeck [11] some years ago and gains support from demonstration of islet-cell hyperplasia in the early or "active" phase of obesity by Ogilvie in man [12] and by Mayer in rats.[13]

It is conceivable, but unlikely, that our observations represent contamination of deep venous samples by blood draining adipose tissue interspersed between muscle fibres rather than metabolism of muscle subjected to unusually large concentrations of endogenous insulin. Examination of arterio/deep-venous (A/DV) and arterio/superficial-venous (A/SV) concentrations of a number of metabolites has revealed a patterned heterogeneity in the human forearm.[14] A/DV differences reflect metabolism of muscle, in the main, and A/SV differences reflect skin and subcutaneous adipose tissue metabolism. Glucose and lactate A/SV differences are greater, whereas O_2, CO_2, and potassium A/SV differences are less than the respective A/DV differences. If contamination by adipose tissue were responsible for the deviations observed in obese subjects, we would anticipate that A/DV differences of all metabolites studied would show the same trend toward resembling A/SV differences. Our studies, however, do not support this, glucose and potassium metabolism selectively differing from controls (table I). Furthermore, negative A/SV differences in the plasma content of free fatty acids in the forearm of obese subjects are reduced to 50% that of controls (0·075 mEq. per litre, compared to 0·127 mEq.).[15] This represents considerable inhibition of the

6. Arendt, E. C., Pattee, C. J. *J. clin. Endocrin.* 1956, **16**, 367.
7. Fraser, T. R. C., Joplin, G. F., Opie, L. H., Rabinowitz, D. To be published.
8. Rabinowitz, D., Asper, S. P., Jr. To be published.
9. Andres, R., Baltzan, M. A., Cader, G., Zierler, K. L. (abstr.) *Amer. J. Physiol.* 1956, **187**, 583.
10. Andres, R., Cader, G., Goldman, P., Zierler, K. L. *J. clin. Invest.* 1957, **36**, 723.
11. Brobeck, J. R., Tepperman, J., Long, C. N. H. *Yale J. Biol. Med.* 1943, **15**, 831.
12. Ogilvie, R. F. *J. Path. Bact.* 1933, **37**, 473.
13. Mayer, J. *J. clin. Nutr.* 1960, **8**, 712.
14. Andres, R., Baltzan, M. A., Zierler, K. L. (abstr.) *Physiologist* 1960, **3**, 9.
15. Rabinowitz, D., Zierler, K. L. Unpublished data.

release of free fatty acids from forearm adipose tissue, an action almost unique to insulin among known humoral agents.

Response of Obese Forearm Muscle to Intra-arterial Insulin

Glucose uptake and change in potassium movement (table II) in response to intra-arterial insulin are significantly less in the obese subjects than in ten healthy subjects of normal body-weight studied previously.[9]

This confirms by a more precise technique earlier observations by Arendt and Pattee and ourselves [6–8] demonstrating "insulin resistance" in obese subjects after intravenous administration of insulin. The full explanation of this phenomenon still eludes us. Any hypothesis must take into account the present evidence for a state of endogenous hyperinsulinism. Hence, although Eckert et al.[16] have presented convincing evidence that cortisol production is increased in obesity, it seems improbable that circulating cortisol can inhibit exogenous, but not endogenous, insulin. A second attractive theory, that "insulin resistance" is a consequence of dilution of a standard dose of exogenous insulin by a large endogenous pool in the obese subject, becomes acceptable only if the plasma level of insulin in obesity is increased greatly, say, by a factor of ten or more, which on clinical grounds is unlikely. Resolution of this problem may possibly be related to the familiar phenomenon in which a tissue, chronically under the influence of excessive amounts of an agent, becomes less responsive to further challenge by the agent.

SUMMARY

1. Enhanced glucose uptake and absence of net potassium efflux from forearm muscle in obese subjects suggests a state of adaptive hyperinsulinism.

2. The respiratory quotient of forearm muscle in obese subjects is 0·7, as in normal muscle, compatible with oxidation of lipid. No quantitative defect in lipid oxidation is therefore present at rest.

3. Intra-arterial administration of insulin produces significantly less glucose and potassium uptake in forearm muscle in obese subjects than in controls. This suggests that tissues which are chronically under the influence of excessive amounts of insulin become less responsible to further challenge by insulin.

These studies were aided by contract Nonr-248 (34) (NR 101-24) between the Office of Naval Research, Department of the Navy, and the Johns Hopkins University, and by Public Health Service Research Grant A-750 and Public Health Service Graduate Training Grant 2A-5232, National Institute of Arthritis and Metabolic Diseases.

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MEASUREMENT OF RENAL BLOOD-FLOW IN THE INTACT KIDNEY BY LOCAL THERMODILUTION DURING HÆMORRHAGIC HYPOTENSION

IN the literature the prevailing view is that hæmorrhagic hypotension gives rise to selective vasoconstriction in the kidneys, among other areas. The term "selective" is used because investigations have shown not only an increase in the calculated renal vascular resistance but a decrease in the calculated renal fraction of cardiac output. The evidence for this, both in laboratory animals [17] and in man,[18 19] was based upon the assumption that *p*-aminohippuric-acid clearance (C_{PAH}) divided by the hæmatocrit is an adequate measure of renal blood-flow. There is evidence, however, that if the rate of urine formation is low—as is the case in hæmorrhagic hypotension—C_{PAH} no longer bears a close relation to direct measurements of renal blood-flow.[20–22] Bálint et al.[23] reported studies of hæmorrhagic hypotension in dogs in which renal blood-flow was measured directly from a cannulated renal vein and cardiac output was measured by the dye-dilution method. These studies showed that blood-flow in the renal vein was far greater than indicated by C_{PAH}, that the renal fraction of cardiac output did not change for some 20 minutes, that renal vascular resistance changed in a manner parallel to total peripheral vascular resistance, and that some degree of selective vasoconstriction in the kidney could be demonstrated only in the later stages of hypotension. Since renal blood-flow appeared to be high throughout, Bálint et al. contested the views of Oliver et al.[24] on the mechanism of development of the "shock kidney".

The development of the local thermodilution catheter [25] has made it possible to investigate this problem without direct trauma to the kidney, and without the errors attending the use of the dye-dilution method to estimate low values of cardiac output.

In 11 dogs under chloralose anæsthesia, one thermodilution catheter was introduced into the right renal vein from the femoral vein, and a second thermodilution catheter was introduced into the pulmonary artery from the right external jugular vein. Blood-pressure was measured from a cannulated femoral artery, and the animals were infused through the left external jugular vein. When urine volume had reached a plateau, the dogs were bled in several stages, some 250 ml. being removed at each stage. After the initial hypotensive reaction to each removal of blood, there was a compensatory rise towards, but not up to, normal values. Measurements were made within ten minutes after each removal of blood, when a new blood-pressure level had been stabilised.

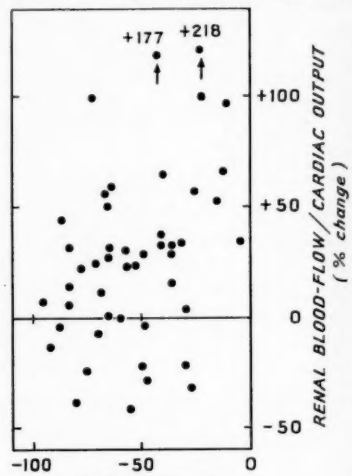

Fig. 1—Change in the renal fraction of cardiac output compared with percentage change in blood-pressure in chloralosed dogs under conditions of acute hæmorrhagic hypotension.

Fig. 1 presents the results in terms of the relative change (from initial values) of the renal fraction of cardiac output as a function of the change in blood-pressure. In only 11 out of 48 measurements was there any decrease in the renal fraction of cardiac output. This fraction rose in the majority of cases. It should be emphasised that this happened even after moderate hæmorrhage, when, although there was a marked fall in C_{PAH}, there was still compensation by the animal. Fig. 2 shows that, far from showing the rise in total renal resistance reported from

16. Eckert, J. P., Green, O. C., Migeon, C. J. (abstr.) 43rd meeting of the Endocrine Society, June, 1961, abstract no. 76, p. 41.
17. Phillips, R. A., Dole, V. P., Hamilton, P. B., Emerson, K., Jr., Archibald, R. M., Van Slyke, D. D. *Amer. J. Physiol.* 1945, **145**, 314.
18. Lauson, H. D., Bradley, S. E., Cournand, A. *J. clin. Invest.* 1944, **23**, 381.
19. Moyer, J. H., Morris, G., Beazley, H. L. *Circulation*, 1955, **12**, 96.
20. Selkurt, E. E. *Amer. J. Physiol.* 1946, **145**, 699.
21. Bojesen, E. *Acta physiol. scand.* 1954, **32**, 39.
22. Bálint, P., Fekete, A., Hajdu, A. *Acta physiol. hungarica*, 1956, **10**, 239.
23. Bálint, P., Kiss, E., Sturcz, J. *Pflüg. Arch. ges. Physiol.* 1961, **272**, 307.
24. Oliver, J., MacDowell, M., Tracy, A. *J. clin. Invest.* 1951, **30**, 1305.
25. Froněk, A., Ganz, V. *Circulation Res.* 1960, **8**, 175.

C_{PAH} calculations, direct measurements showed that in most animals this parameter was directly related to blood-pressure. The shape of the regression line suggested by the results in fig. 2 indicates that autoregulation of renal blood-flow in response to a change in perfusion pressure[26–28] may also exist even under the above conditions.

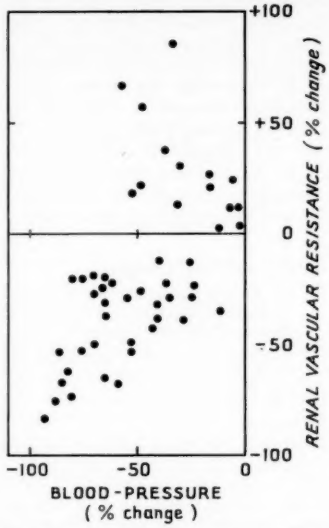

Fig. 2—The relation between percentage change in calculated total renal vascular resistance and percentage change in blood-pressure.

It is doubtful, however, whether these results can be taken as evidence against the ischæmic origin of the "shock kidney", since P.A.H. extraction in these experiments decreased in a parallel fashion to renal blood-flow and rose promptly with replacement of blood or an equal volume of iso-oncotic dextran. To test this further, renal cineradiography was carried out before and during hypotension by injecting 60% 'Urografin' into the aorta above the origins of the renal arteries. Standard diameters across the perfused area in the kidney, during the "capillary" phase of the arteriograms, were measured from the cinematographic pictures, in reference to the known width of the catheter. The table shows that the diameter of the perfused area of the kidney decreased by about 10% during hypotension, which corresponds to the width of the cortex in the dog kidney.

The most likely explanation for these findings is that arteriovenous shunts have opened up early in the stage of acute hypotension, blood being excluded from the cortical circulation. This old concept[29] has been more recently elaborated in detail by Trueta et al.,[30] and most vigorously

DIAMETER OF THE PERFUSED PORTION OF THE DOG KIDNEY DURING INTRA-ARTERIAL CINERADIOGRAPHY

Two diameters were measured by taking a constant angle from the end segment of the catheter, and all measurements were corrected to absolute values from the known width of the catheter. Figures are average ± S.D.

—	Diameter 1 (mm.)	Diameter 2 (mm.)
Control period	37·16 ± 0·78	43·71 ± 3·44
Hypotension	33·40 ± 1·26	38·37 ± 0·67

contested by a large number of investigators (e.g., Maxwell et al.[31]) who have argued that such a mechanism might exist only under extremely pathological conditions, and even then only in the rabbit. Anatomical evidence for the opening of shunts during acute hypotension has recently been presented by Gömöri.[32]

The present data suggest that: (1) particularly under conditions of reduced perfusion pressure, C_{PAH} is in fact only a measure of the supply of blood to the proximal tubule, where it is secreted; and (2) of the possible aglomerular blood paths through the kidney, arteriovenous shunting may be a more physiological mechanism, and applicable to more mammalian species, than has been previously considered, since it occurred under conditions of acute hypotension which cannot be equated with shock.

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26. Winton, F. R. Modern Views on the Secretion of Urine; p. 61. Boston, 1956.
27. Pappenheimer, J. R., Kinter, W. B. *Amer. J. Physiol.* 1956, **185**, 377, 391.
28. Hardin, R. A., Scott, J. B., Haddy, F. *Amer. J. Physiol.* 1960, **199**, 1192.
29. Gross, C. F. Essai sur la structure microscopique du rein. Strasbourg, Paris, Geneva, 1868.
30. Trueta, J., Barclay, A. E., Daniel, P. M., Pritchard, M. M. L. Studies on the Renal Circulation. Oxford, 1947.
31. Maxwell, M. H., Breed, E. S., Smith, H. W. *Amer. J. Med.* 1950, **9**, 216.
32. Gömöri, P. (1960) First International Congress of Nephrology, abstract of papers, *Excerpta Med.*, international congress series, no. 29.

New Inventions

TAPERED NYLON-REINFORCED-LATEX ENDOTRACHEAL TUBES

THE rigidity of the wall of a reinforced-latex tube limits the possible size of the connector. This means that the lumen is unnecessarily reduced, unless a larger connector is inserted into the flaccid proximal (machine) end of soft latex. In that case, however, the tube length cannot be adjusted; furthermore, the junction itself is a weak point because kinking is likely.

I have introduced tapered tubes which have two advantages: (1) a larger connector can be used; and (2) the length is adjustable, since the tube can be cut. This does not weaken it; and it will still withstand boiling. The tubes, of latex, are reinforced by a nylon helix. This runs the whole length of the tube, and there is no flaccid section of latex at the proximal end. The metal connector (which can be of any type) thus fits against a rigid wall (fig. 1).

The following sizes (Magill scale) are available: plain tubes, 1–10; cuffed tubes, 3–10. These refer to the distal (patient)

Fig. 1.

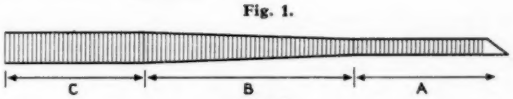

Fig. 2.

end. The tubes are tapered so that one of two connectors will fit them all. Sizes 1–6 have a distal end 2 in. long, a 3 in. tapered middle piece, and a proximal end, 2 in. or longer, of size 7 (Magill scale). In sizes 7–10 the distal end is 3 in. long, the tapered centre piece 4 in., and the proximal end (size 11) 2 in. or longer (sections A, B, and C in fig. 2).

The internal and external diameters at either end of the tube conform to the specifications and manufacturing tolerances for Magill tubes in extruded natural rubber, and so do the sizes of the cuff and inflating tube.

We have used our tubes for some time; they have proved entirely satisfactory. They should be cleaned with soap, water, and a brush, and then boiled for three minutes to sterilise them.

The tubes have been developed by the British Oxygen Company, and can be obtained from A. Charles King, Devonshire Street, London, W.1.

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Reviews of Books

Medicine and the Navy 1200-1900

Vol. III: 1717–1815. CHRISTOPHER LLOYD, F.R.HIST.S., assistant professor, Royal Naval College, Greenwich; Surgeon Captain JACK L. S. COULTER, F.R.C.S., Royal Naval Medical School. Edinburgh and London: E. & S. Livingstone. 1961. Pp. 402. 50*s*.

WHEN the first part of the late Surgeon Commander John Keevil's history of medicine in the Royal Navy appeared, no comparable study existed. Indeed, the subject had been so neglected that even in the standard eight-volume history of the Navy the name of James Lind, "the father of nautical medicine", appeared only once—and was then misspelt, and in an erroneous context. So completely did the new work deal with its period that it was received with warm approval everywhere: and the death of its author while preparing the succeeding volume for the press was mourned by many more than his personal friends.

The sponsors of this history, the Wellcome Trustees, have now fortunately commissioned Mr. Lloyd and Surgeon Captain Coulter to complete it, and it is they who have compiled this volume. This covers the critical century when British seapower was challenged in places as far apart as Batavia and Quebec, Walcheren and the Nile. This was the time also when the foundations of present naval medical practice were laid, and so the authors have adopted for the book a different pattern from that found in its predecessors. One section of six chapters describes each of the major campaigns: another is devoted to the founding of the naval hospitals: and a third considers individually the important causes of disease in ships of the day. In every other respect, including the high standard he set, the new volume compares closely with those Commander Keevil wrote.

One chapter in particular will be widely read, even by those unconcerned with the subject of the book as a whole. It deals with Nelson's experience of his surgeons, which was unusually intimate. For the admiral was, with one exception, wounded in every engagement in which he participated. The stump of his right arm took a very long time to heal, and his loss of sight in one eye was accompanied by so much damage to the other that Beatty believed that only his death averted an impending total blindness. It is not surprising that Nelson should have been so conscious of his own mortality that he kept in his cabin a coffin, and a puncheon of rum for the preservation of his body.

The Biology of Space Travel

Symposia of the Institute of Biology no. 10. Editor: N. W. PIRIE, F.R.S. London: Institute of Biology. 1961. Pp. 120. 25*s*.

THIS symposium, held in September, 1960, was, of course, very much pre-Gagarin: but since it concerned itself with biological fundamentals and with ideas rather than technological detail, its discussions have not been dated by two major and two minor excursions into Space. Many of the papers have something of an academic air, as if the subject were interesting but remote: but in this country any discussion on Space can only be academic at present, and an academic discussion is better than none. There are also one or two moral judgments, which seem out of place in a symposium on biology.

For its size, the book covers the subject very well, and its economy of words is an example to more ambitious works. Nor does it confine itself to descriptions of phenomena or to speculations of what might be termed the first degree: there are a number of entertaining ideas which, even if they are not all intended to be quite serious, open up fascinating lines of thought. There is a suggestion, for example, that it may one day be possible to connect an astronaut to the electrical system of his ship in order to restore his energy by means more direct than old-fashioned nutrition; or that autotrophic organisms, which have been trained to use electrical energy for their metabolic drive, may form an important part of an astronaut's food. Whatever attracts the adventurous to Space travel, it seems unlikely, either now or in future, to be the diet. There is an interesting description of the methods used to select American astronauts. One wonders, indeed, that after so onerous an examination, any attractions remain for the chosen, who are evidently men of some determination.

The book is well produced and fully indexed. It is recommended to anyone whose interest in Space medicine goes beyond the superficial or the sensational.

Leukocyte Agglutinins

SVEN-ÅGE KILLMANN, M.D., Brookhaven National Laboratory, Associated Universities Inc., Upton, Long Island. Oxford: Blackwell Scientific Publications. 1960. Pp. 96. 20*s*.

THIS monograph is a comprehensive review of the literature which has accumulated in the eight years since leucocyte agglutinins were first reported. The author describes the technique he now uses for detecting these agglutinins, but apart from this the book contains no original observations. Dr. Killmann does, however, refer to his earlier publications in the appropriate places in the text. Leucocyte agglutinins in human beings are not known to arise naturally; they are commonest in persons who have had blood-transfusions; they sometimes appear in or after pregnancy; they have been detected in patients with collagen diseases, leukæmia, Hodgkin's disease, cirrhosis of the liver, and some virus infections; and they have been found in the serum of patients with agranulocytosis due to drugs. The evidence for all these types of leucocyte agglutinins is faithfully recorded and critically discussed. Dr. Killmann thinks that many of the published reports have shortcomings and that repetition by more careful methods is quite often desirable.

The A, B, and O antigens of red cells and some others are present in white cells, and they seem also to have antigens of their own that may be hereditary. It is known that leucocyte agglutinins may be responsible for transfusion reactions, and blood banks are beginning to take an interest in leucocyte grouping. This book should certainly be consulted by anyone contemplating work in this subject.

The Adrenal Cortex

The Proceedings of a Symposium organised by the Association of Clinical Pathologists held in London on Oct. 14–15, 1960.—Editors: G. K. MCGOWAN, M. SANDLER. London: Pitman Medical Publishing Co. 1961. Pp. 226. 25*s*.

THIS book, the first of a series relating chemical pathology to clinical medicine, reports the proceedings of a symposium on the adrenal cortex at which the application of biochemical tests of adrenocortical function to the diagnosis and treatment of adrenal syndromes was discussed. The expert contributions on the anatomy and physiology of the adrenal cortex, the chemistry and pharmacology of its hormones, and the methods for their estimation in body-fluids in the known adrenocortical disorders provide an up-to-date and inexpensive guide to this increasingly complex and important subject. A useful appendix unravels the mysteries of the nomenclature and chemistry of the adrenal hormones for the uninitiated. Clinicians interested in the adrenal must read this book, which should be found in every hospital biochemistry laboratory.

A Text-book of Midwifery (18th ed. London: A. & C. Black. 1961. Pp. 592. 45*s*.).—In this popular work by Prof. R. W. Johnstone, now revised in collaboration with Prof. R. J. Kellar, text and illustrations have been thoroughly renewed and certain sections have been completely rewritten. In the chapter on forceps it is pleasing to find emphasis on the description of low rather than mid forceps delivery. The section on radiology refers to the importance of minimising fœtal radiation without sacrificing diagnostic accuracy. Student and general practitioner will find here a balanced and accurate account of modern obstetric practice.

THE LANCET

LONDON 23 SEPTEMBER 1961

Doctors for the Forces

WITH alarming rapidity this country's Armed Services are running short of doctors; and *The Times*[1] has done well to draw public attention to this—the sharpest manifestation so far of a growing national problem. The Platt report[2] indicated how far the civilian hospital service relies on overseas graduates (who fill more than one in three of the junior posts); and the steep decline in the numbers of doctors applying for general-practice vacancies is further evidence that events have upset some of the forecasts in the Willink report.[3,4] Whatever the final solutions to the general shortage of doctors, the difficulties of the Armed Forces must be overcome soon or there will be a breakdown that would impose serious limitations on the deployment and function of the three Services; for no unit can move far without its doctor. The R.A.M.C. is the most severely threatened, and sooner or later the pressure of shortages here and elsewhere in the Service, together with changes in policy, may lead to a reconstruction of the Army and a reduction of its commitments. Certainly it now seems redundant to hold in readiness any machinery for raising and administering a very large Army. By concentrating further on small mobile formations, the gap between requirements and men available may be narrowed.

Meanwhile, if it is accepted that their present strength must be maintained, the Services require about 175 new doctors each year: 25–30 for the Navy, about 100 for the Army, and 40–50 for the Royal Air Force. The last National Service doctor was called up last November, and, in an effort to restore the supply of medical officers, large financial inducements in the form of tax-free gratuities were offered in May this year—£1500 and £3000 for three-year and five-year commissions respectively. But it is reported (and not denied) that since then only one doctor has joined the R.A.M.C., and very few more have gone into the other two Services. Quite soon, therefore, and possibly before that last National Serviceman is released in November, 1962, all three medical departments will be hard pressed to meet their commitments, and the R.A.M.C. may face an actual breakdown. The imminence and severity of the crisis may have been disguised by optimistic forecasts of how many doctors would be attracted by the new offers; certainly the situation that *The Times* disclosed must have surprised many readers. And some may have wondered whether a similar emergency might soon embarrass the National Health Service as well.

What makes Service life unattractive to young doctors? The chief reasons given, both publicly and privately, by the most articulate, are: lack of clinical interest; instability, because of postings here and there; inadequate quarters for married officers; poor working environment; and loss of the clinical freedom to which they were accustomed, particularly in the matter of what drugs may be used. A few mention that their seniors in the middle grades do not seem so well off financially as civilian doctors of the same seniority. Hardly any regard junior officers' pay as inadequate, though many say it is not enough to outweigh the disadvantages of a Service career. Significantly, few complaints are heard from specialist officers, and shortages in this group are said to be trivial compared with those in the general-duty branches. There is discontent, too, among middle-range regular officers, judging from the numbers who are said to be seeking premature retirement: relatively poor pay and instability seem to be the main causes.

Some of these defects may be remediable. More might be done to make the Service general practitioner's work more satisfying, though his "list", being relatively young and healthy, will always produce less serious and less varied illnesses than his civilian colleague sees. It is seldom desirable to treat sick men in barracks, especially when it is relatively easy to put them in a sick-bay; and more station sick quarters on the R.A.F. style might make Service general practice more attractive. Here the College of General Practitioners might have some good advice to give. Stability in postings is easier to achieve when the units with which the doctors serve are themselves stable—and that cannot always be so. Unhappily, as the number of Service doctors declines so stopgap postings may increase and aggravate the situation. At the best, some enforced mobility is inescapable for a member of the Armed Forces; but it is widely believed that much more could fairly be done to avoid unnecessary disturbance. Quarters are very important to a profession that often gets married, and a guaranteed or "tied" quarter could be provided for the doctor wherever he goes. And his freedom to prescribe should be made just as wide as the needs of the Service allow.

When all possible improvements have been achieved, however, many drawbacks to Service life will persist, and if the young doctor is to be attracted into the Services, the disadvantages must be acknowledged, not disguised, and a sufficient inducement over his civilian expectation must be offered to overcome them and to dispel any fear that his contemporaries will think poorly of him for choosing a Service career. There is much to be said for basing the Service doctors' pay code on the current earnings of general practitioners, as assessed by the Ministry of Health, plus whatever betterment factor is required to overcome the less attractive features of Service life. This, after all, is how large industrial firms who need doctors in unattractive places find their recruits: they pay the market price.

1. *Times*, Aug. 15 and Sept. 8, 1961.
2. Medical Staffing Structure in the Hospital Service: Report of the Joint Working Party. H.M. Stationery Office, 1961. See *Lancet*, 1961, i, 649, 657.
3. Report of the Committee to Consider the Future Numbers of Medical Practitioners and the Appropriate Intake of Medical Students. H.M. Stationery Office, 1957.
4. Lafitte, F., Squire, J. R. *Lancet*. 1960, ii, 538.

Another solution (or part of a solution) is a return to conscription or selective service (involving a random selection, by ballot from newly registered doctors, of the number needed to meet minimum Service needs). The strongest opposition to such plans might come from those who are already alarmed by a decline in the demand for places in British medical schools—a decline which shows what some parents and children are thinking about medicine as a career at the very time when the country needs more doctors. Medical conscription, without general conscription, might produce a further damaging drop in entries to medical schools.

It has been said that, for the care of men and dependants in the United Kingdom, the Services could rely wholly on the National Health Service, possibly with a wider use of their own auxiliary medical staff. But the objection is that this would leave medical officers to serve only overseas, thus driving many out of the Services and discouraging recruitment. Moreover, it is doubtful whether enough civilian doctors could be found to undertake the general duties in home military establishments, to say nothing of those overseas where help is most needed. Unification between the three Services might further economise in specialist manpower, but it would not do much to fortify the ranks of general-duty officers. Nevertheless, these and other remedies must now be urgently re-examined, if a useful number of doctors are to be recruited from those who will be registered next January. And the profession should not look upon this shortage as a detached and confined problem. What is perplexing the Ministry of Defence today may well alarm the Ministry of Health and the whole country tomorrow.

Endometriosis

THE pathological state which results from the development of ectopic endometrium was first reported towards the end of the 19th century by VON RECKLINGHAUSEN and by CULLEN. But SAMPSON [1] in 1921 gave the classical description of the disease, now known, at BLAIR BELL'S [2] instigation, as endometriosis. In the past thirty years endometriosis has taken an increasingly large place in gynæcological practice; but whether this is due to commoner recognition or a true increase in incidence under the stresses and restraints of modern life is debatable.

Until 1958 the treatment was almost entirely surgical. Hormone therapy by œstrogens had been suggested, chiefly as a diagnostic test, by MEIGS [3]; and it was recognised that androgens might provide palliation in some cases; that the menopause, whether natural or artificial, usually resulted in cure; and that pregnancy often brought about remarkable improvement or even complete cure. The synthesis of the newer, highly potent, progestogens revived interest in the possibility of palliation and even cure by producing a pseudo-pregnancy reaction, and KISTNER [4] and others have reported favourably on their value. RIVA et al.[5] have further strengthened the argument for conservative treatment by a study of the effects of norethynodrel in 123 patients.

In the majority the diagnosis was made by culdoscopy, but in a small minority by laparotomy with conservative surgery. These workers remark on the inaccuracy of the preoperative clinical diagnosis of endometriosis, which was correct in only 54% of a large group of cases previously reported by them.[6] A special endometriosis clinic was established for regular review and treatment after initial visual diagnosis, and the extent of the disease was graded according to the number of pelvic structures involved. (This somewhat arbitrary classification is perhaps the only real weakness in their study; for it might be argued that multiple small deposits with slight surrounding tissue reaction indicate less severe disease than gross involvement of a single appendage, with extensive adhesions and fibrosis.) After treatment 78% of their patients showed no evidence of endometriosis at culdoscopy or laparotomy, and a further 10% showed improvement. Norethynodrel was given continuously, over an average period of 5·8 months, in increasing dosage—in some cases up to 100 mg. daily. In a few cases treatment was continued for more than six months; and, as might be expected, in these the cure-rate was less satisfactory, indicating greater resistance or more advanced disease. Regression of the endometrium to a relatively atrophic state with distinct stromal decidual reaction was observed in all cases, and decidual reaction in endometrial deposits on the bowel was clearly demonstrated. Undesirable side-effects, similar to, though more pronounced than, symptoms often arising in pregnancy were sufficiently troublesome for patients to need considerable persuasion to persevere with treatment for six months. These side-effects included variations in libido, abdominal cramps, break-through bleeding, and nervousness and irritability. 5 patients became so severely disturbed that psychiatric treatment was necessary—which prompts RIVA et al. to suggest that there is a neurotic personality type in which endometriosis is especially liable to develop—a suggestion which many practising gynæcologists will endorse. In a few cases myomas enlarged rapidly during treatment, but these regressed when treatment was discontinued. That function of the genital tract was not permanently inhibited was shown by the rapid return of normal menstrual rhythm, and by subsequent pregnancy in 4 patients, each of whom had previously been infertile for some time.

It is still debatable whether endometriosis can be permanently cured by hormone therapy: insufficient time has elapsed for firm conclusions from the series reported; but of 28 patients who were followed for an average of eleven months recurrence took place in 5 (18%) after remission lasting on average 7·2 months. In 4 of these cases the recurrence affected organs other than those involved on the first occasion; and this

1. Sampson, J. A. *Arch. Surg.* 1921, **3**, 245.
2. Bell, W. B. *J. Obstet. Gynæc. Brit. Emp.* 1922, **29**, 443.
3. Meigs, J. V. *Ann. Surg.* 1941, **114**, 866.
4. Kistner, R. W. *Amer. J. Obstet. Gynec.* 1958, **75**, 264.
5. Riva, H. L., Wilson, J. H., Kawasaki, D. M. *Amer. J. Obstet. Gynec.* 1961, **82**, 109.
6. Riva, H. L., Hatch, R. P., Breen, J. L. *Obstet. Gynec.* 1958, **12**, 610.

observation (though on only a small number of cases) supports to some extent the view that the individual lesions of endometriosis are self-limiting, and that so-called " recurrences " are really fresh developments of endometriotic tissue, resulting from continued basic predisposition (whatever that may be) and continued ovarian activity. Much further study, controlled by biopsy before and after treatment, will be needed to establish whether progestogens should have a major place in the treatment of endometriosis or whether they should be regarded as a useful adjunct to surgery and, in younger women, as a means of palliation that may make pregnancy possible. JEFFCOATE [7] categorically stated that progesterone therapy was surprisingly disappointing, but the newer synthetic compounds may possibly have an effect lacking in progesterone itself. Cyclical treatment, on which GRANT [8] reported favourably, and which has the advantage of preserving withdrawal bleeding and minimising the unpleasant side-effects, may prove as valuable as continuous treatment. A lapse of at least five years after the conclusion of treatment, whether cyclical or continuous, is necessary before the results can be finally evaluated.

Staphylococcal Pulmonary Infection

IT is easy to isolate staphylococci from a great many places in hospitals as well as from patients and staff. The difficult thing, even with the help of phage-typing, is to assess the clinical significance of the organisms isolated.[9] Nevertheless, a composite picture is being gradually assembled from the numerous published accounts of such episodes of hospital infection as have been sufficiently studied to permit of reasonable deductions about their probable origin and mode of spread. Among all this work, the human lung has not been forgotten as an important site of infection [10 11] for the individual patient, but its significance as a major reservoir and source of hospital infection has probably not had enough attention.[12] Staphylococci which establish themselves in a patient's lung have a good opportunity to increase in number, to become adapted to growth in human tissue, and to be widely disseminated by the coughing of the sufferer. In our present issue Mr. MITCHELL and his associates report on the pathology and bacteriology of the lungs examined at 150 consecutive necropsies at Law Hospital in Lanarkshire during a year in which there were 575 deaths in the hospital. On strictly pathological grounds, and without knowledge of the bacteriology, a diagnosis of lung sepsis was made in 60 of the 150 cases (40%). In deaths eight or more days after admission, the incidence was 50%. The diagnosis of lung sepsis rested on the detection of such obvious lesions as bronchopneumonia or lung abscess or on the histological demonstration of purulent exudate in the alveoli. Hæmorrhages and infarcts were not classed as evidence of lung sepsis unless there was concomitant bronchopneumonia. When the bacteriological and pathological findings were examined together, it became clear that lung sepsis in patients dying more than a week after admission was predominantly a consequence of, or at least associated with, staphylococcal infection by an organism acquired in hospital. Pre-existing lung disease—not uncommon in patients from Lanarkshire—was an important predisposing influence favouring the onset of lung sepsis in hospital.

From routine spleen cultures, made at necropsy, staphylococci were isolated in 20 cases. There was a positive lung culture of the same strain in each of these cases, and 17 had frank lung sepsis. In no case was a positive spleen culture obtained from a subject who did not also show a positive lung culture. SMITH et al.[13] have already concluded that the lungs are a common primary focus for septicæmia—a conclusion of obvious importance even if the present evidence in support of it may be diminished by the possibility that invasion of the bloodstream from the lungs may have been only a terminal phenomenon in some of the cases. MITCHELL and his colleagues cite details of individual cases to support their view that blood-borne staphylococcal infection from the lungs may account for some of the postoperative complications of abdominal surgery, such as local peritonitis, rupture of suture lines, and even wound sepsis. In 5 of the postoperative deaths, they believe, hospital-induced lung sepsis could be regarded as the primary cause of death; and in their whole series they think that lung sepsis was the primary cause of death in 9 of the 47 cases dying with overt lung sepsis.

Clearly this is an important contribution to our current thinking about the staphylococci in hospitals. It would be useful if other similar studies could be made in different parts of the country to disclose whether a similar state of affairs is general or is somehow the outcome of particular local conditions. Even without confirmatory evidence, however, we should obviously note that patients with chronic chest disease may run a special risk in a general hospital and may become a heavy source of infection to others. This raises the need for clear thoughts about a policy to make isolation possible for such patients. No doubt the judicious use of penicillinase-resistant penicillins would have a valuable place in the management of such patients. Obviously also their stay in hospital should not be unnecessarily prolonged. Another point of obvious importance is that hospital ventilation systems, especially those now being planned for new multi-storey hospitals, will need to be made the subject of careful study, not by architects and engineers only but also by medical men and nurses. In this connection we may have much to learn from the experience of those who knew the problems of the old " fever hospitals ". The problems to be solved do not seem to be at all easy; and it is quite certain that they will not solve themselves.

Above all, perhaps, we still need to adjust many of our instinctive attitudes towards hospital sepsis. Too often

7. Jeffcoate, T. N. A. Principles of Gynæcology. London, 1957.
8. Grant, A. Personal communication.
9. Williams, R. E. O., Blowers, R., Garrod, L. P., Shooter, R. A. Hospital Infection: Causes and Prevention. London, 1960.
10. Brownrigg, G. M. *Canad. med. Ass. J.* 1955, **73**, 787.
11. Gresham, G. A., Gleeson-White, M. H. *Lancet*, 1957, i, 651.
12. Shooter, R. A., Griffiths, J. D., Cook, J., Williams, R. E. O. *Brit. med. J.* 1951, i, 433.
13. Smith, I. M., Vickers, A. B. *Lancet*, 1960, i, 1318.

investigation still seems to be hindered by reluctance of some nurses and doctors to admit that infection exists or that it really matters. Admittedly, records of sepsis are kept more commonly than they once were, but too often they are so poorly kept and so uninformative that the whole truth about particular situations is concealed rather than revealed. Those who make investigations must for their part be careful to keep away any atmosphere suggestive of witch-hunting. Hospital infection will be most effectively tackled by admitting its presence, recognising its inherent interest, trying to work out sensible solutions, and avoiding a search for scapegoats. Hospital sepsis as a problem belongs to all of us; and we need to tackle it with our best human good will as well as with our technical methods and brains.

Annotations

THIOPROPERAZINE

THE development of further neuroleptic agents—particularly the phenothiazines—shows no sign of slackening. In this series the earlier drugs tended to be soporific; but with substitution of a piperazine group (producing prochlorperazine, trifluoperazine, &c.) their tranquillising action became more powerful. When they were also found to have more side-effects—especially on the extrapyramidal system—it was suggested that these might be a necessary indication of therapeutic action, which would not exist without them. Strong support for such a correlation now comes from Denham and Carrick's investigation [1] of thioproperazine ('Majeptil'). This drug is identical with prochloperazine, except that the chlorine atom has been replaced by a dimethyl sulphamoyl group. The frequency of neurological side-effects is high, and Delay et al.[2] had already proposed that these could be directly related to the degree of therapeutic efficacy in schizophrenia and acute mania.

Denham and Carrick treated 60 patients who had failed to respond to previous measures, and 58 of these were chronic schizophrenics—some with florid symptoms but others largely vegetative. In view of the drug's therapeutic potency and its side-effects, comparison with placebo was not considered worth while; and, after a drug-free interval, the patients were used as their own controls. Of the schizophrenics, 32 achieved total remission of their symptoms, 10 became able to play an active part in the life of the hospital, and 15 no longer presented nursing problems: only 1 (previously leucotomised) showed no improvement. The 2 manic patients also "responded adequately". There was rapid lessening of hallucinations, delusions, apathy, and behaviour disturbances, while suggestibility was increased, permitting help by psychotherapy. Most cases were treated by Delay's "discontinuous" method, in which the optimal dose is given for several periods of five days, with intervals between.

Though these results certainly seem impressive, the greater part of the report is devoted to analysis of the neurological effects of thioproperazine. These fall into three main syndromes (described as the akinetic, akinetohypertonic, and hyperkineto-hypertonic states) which closely resemble the effects of epidemic encephalitis; they may be accompanied by autonomic disturbances and changes in the level of consciousness. The most important single symptom was muscular hypertonus, whose degree and extent are said to be correlatable with the degree of psychiatric improvement. In explanation, it is suggested that both this drug and the virus of von Economo's disease disturb the reticular substance, since experimental damage to this area has similar consequences. This action is further postulated to have a favourable influence on centres involved in the schizophrenic process—though no conclusions are drawn about the ætiology of schizophrenia. Rinaldi and Himwich [3] had earlier suggested that chloropromazine and reserpine modify both motor and mental functions by acting on the reticular activating system.

In their letter on p. 720, however, Dr. Luke and Dr. Wyllie say that, given intravenously, thioproperazine has proved valuable as a non-specific tranquillising agent for disturbed behaviour. The various somatic effects were found to follow a regular time sequence, but extrapyramidal features were unusual and came some time after the therapeutic "calming" action. The explanation offered by Luke and Wyllie is that there are various sites of action, which the drug reaches at different times.

Reports of any new tranquilliser are likely to induce a feeling of déjà-vu, since it always appears that dramatic cures have been achieved in patients who have failed to respond to any previous treatment. The reader is rarely able to judge whether the previous treatments were given at an effective dosage level and for a long enough time. It is also hard to understand why drugs which have no great qualitative difference (such as the phenothiazine series) should produce widely divergent results; and one wonders how far the divergence is due to differences of dosage. To decide what the dose should be is by no means easy, since the various forms of pharmacological testing are of doubtful value as guides to what is needed for patients. Thioproperazine, for instance, is 150 times more potent than chlorpromazine—if one judges by anti-apomorphine tests in dogs and the production of akinesia and catalepsy in the rat [4]; yet the relative dosages used show nothing like this comparison. Drug trials also very often lack adequate data on the length of subsequent remissions.

The hypothesis of Denham and Carrick is attractively simple; and we may suppose it very likely that the phenothiazines act in some way through the reticular formation. But the fact that two phenomena can be correlated does not prove that one is the cause of the other. Similar detailed correlations were made at one time between the somatic effects of insulin and its presumed benefits in schizophrenia. The "shock" effect of intermittent treatment with thioproperazine also seems open to question; and we must all wish to guard against the development of a new mythology.

UNUSUAL CANCER IN ULCERATIVE COLITIS

PATIENTS with ulcerative colitis seem to have a predilection for carcinoma of the large intestine—an important fact not only when considering treatment of ulcerative colitis but also as a possible clue to the origins of cancer itself. Now it seems possible that the predisposition may be to malignant change generally and may not be

1. Denham, J., Carrick, D. J. E. L. *J. ment. Sci.* 1961, **107**, 326.
2. Delay, J., Deniker, P., et al. *Pr. méd.* 1959, **67**, 201.
3. Rinaldi, F., Himwich, H. E. *Dis. nerv. Syst.* 1955, **16**, 133.
4. Courvoisier, S., Ducrot, R., Farnel, J., Julai, J. 5th Congress of Psychiatry and Neurology, Strasbourg. July, 1958.

confined to epithelium alone; for Cornes et al.[1] describe two cases of lymphosarcoma arising in the large intestine affected by chronic ulcerative colitis and refer to five similar cases previously reported.

The sceptic could argue that lymphosarcoma as a primary disease of the intestine, albeit rare, simulates ulcerative colitis in its pseudopolypoid form, and that it might be all too easy to fall into the error of concluding that the two conditions coexist. Cornes et al. have been careful to avoid this error; in both their patients the inflammatory disorder had existed for considerable periods (11 years and 16 years) before lymphosarcoma developed and was diagnosed—a latent period strikingly similar to that preceding the development of carcinoma. Moreover in one patient there was also the quiescent period associated with the "burnt-out" disease, so deceptive to the clinician who feels that all must now be well but later finds advanced bowel carcinoma. Moreover primary malignant lymphoma, lymphosarcoma, or reticulosarcoma of the intestine usually presents throughout the gastro-intestinal tract[2]; but, as far as can be ascertained, in the cases of chronic ulcerative colitis this form of malignant change affected the large intestine, the small intestine remaining clear though metastatic deposits were found in regional lymph-nodes, liver, and lungs. In fact the true nature of the obvious malignancy in the colitis group was not revealed until specimens were examined microscopically; by contrast the laparotomy appearances in primary intestinal lymphosarcoma are sufficiently bizarre to arouse suspicion in the surgeon's mind that this is not an ordinary case of carcinoma.

Cornes et al. believe that, since primary lymphosarcoma of the intestine is so rare, its discovery, even though reported only seven times, in ulcerative colitis may represent more than a chance association; but they rightly emphasise that this is a guess rather than a certainty.

UNREST ON THE WARD

SINCE hospitals became a national responsibility there has been growing awareness that precedent and tradition are poor guides by which to run them for the patients' benefit. The report on the organisation of the patients' day,[3] which suggested wide changes to make hospital treatment more comfortable, met with a warm response from the public; and in the House of Commons [4] severe criticism has been expressed on such topics as noise,[5] maternity routine, appointment systems, waiting-lists, morale, communication with relatives, visiting hours for children, major operations carried out by junior staff, and even the design of artificial limbs.

Some of the avoidable defects in arrangements for the patient's comfort and contentment may derive from less-than-perfect relations between the staff. Prof. R. W. Revans [6] questioned 622 sisters from nineteen hospitals and showed (not surprisingly perhaps) that turnover of junior nurses reflected the extent to which the sisters were flexible or authoritarian in attitude, and that the behaviour of the sisters was patterned by their attitude towards the hospital administration as a whole: aloofness or hostility at the top was transmitted all the way down. Patients, it seemed, stayed longer in hospitals that could not keep their staff.

Approaching ward problems from the patients' point of view, Mrs. McGhee [7] interviewed a random sample of 200 patients before and after discharge from a thousand-bed teaching general hospital in Edinburgh. Patients regarded 12–15 beds as the optimal number for a ward, even professional people enjoying the community atmosphere: "group morale" was experienced by patients and seemed therapeutic. Greater flexibility and quantity of visiting was the amenity patients wanted most of all. Patients disliked rigid nursing routine, especially over bedpans and in the early morning; and their need for closer emotional support was implicit in their pleas for "patient" rather than "duty" assignment and their regret at staff mobility. Technical procedures were little questioned, but nurses doing non-nursing and unskilled domestic duties evoked adverse comment—again because these interfered with actual "nursing". Comments on medical care were directed at manner rather than matter, with especial pleas for more regular information on treatment and progress. "Communication" was indeed the major bone of contention, and on this two patients out of three expressed dissatisfaction. After discharge patients noted a sort of therapeutic "no-man's-land" between hospital and domiciliary services, indicating a need for closer liaison.

DIAGNOSIS OF GONORRHŒA

THE demonstration of intracellular gram-negative bean-shaped diplococci in stained smears of urethral secretion is usually accepted as sufficient evidence on which to diagnose and treat gonorrhœa in the male. In the female, diagnosis is more difficult: examination of stained smears is less reliable than cultural methods, which moreover permit full identification of the gonococcus. It has long been known that other members of the neisseria group may sometimes be found in the genital tract, especially in females, and may lead to confusion with the gonococcus unless isolated and fully identified by fermentation reactions. The occurrence of *N. meningitidis*,[8] *N. flava*,[9] and *N. catarrhalis* [10] was described by earlier workers. Wax [11] examined 492 cultures of neisseria isolated from male and female patients after they had been treated for gonorrhœa with penicillin and found that 19% had biochemical properties which differentiated them from the gonococcus. Most of these organisms were identified as *N. sicca*. Wax said that "not a single profuse purulent urethral discharge in the male revealing intracellular gram-negative diplococci with flattened adjacent sides proved on cultivation to be neisseria other than the gonococcus". Johnston [12] examined 43 strains of neisseria isolated from the urogenital tract and thought not to be gonococci because of their colonial appearance; 31 proved to be *N. sicca* and 12 *N. subflava*. Wilkinson [13] examined 327 strains of neisseria from the urogenital tract and found 6 strains of *N. flava*, 5 of *N. catarrhalis*, and 2 of *N. sicca*.

1. Cornes, J. S., Smith, J. C., Southwood, W. F. W. *Brit. J. Surg.* 1961, **49**, 50.
2. Cornes, J. S. *Cancer*, 1961, **14**, 249.
3. The Pattern of the In-Patient's Day. Central Health Services Council. H.M. Stationery Office, 1961. See *Lancet*, 1961, i, 706.
4. *Hansard*, July 11. See *Lancet*, July 22, 1961, p. 216.
5. See *Lancet*, Sept. 9, 1961, p. 590.
6. Revans, R. W. Measurement of Supervisory Attitudes. Obtainable from the hon. secretary of the Manchester Statistical Society, F. S. D. Ltd., 6, St. James's Square, Manchester, 2, for 7s. 6d.
7. The Patient's Attitude to Nursing Care. By ANNE MCGHEE, A.M.I.A., Nursing Studies Unit, University of Edinburgh. Edinburgh: E. & S. Livingstone. 1961. Pp. 96. 10s. 6d.
8. Carpenter, C. M., Charles, R. *Amer. J. publ. Hlth*, 1942, **32**, 640.
9. Carpenter, C. M. *ibid.* 1943, **33**, 135.
10. Hendriksen, S. D. *Acta derm.-venereol., Stockh.* 1945, **26**, 506.
11. Wax, L. *J. vener. Dis. Inform.* 1949, **30**, 145; *ibid.* 1950, **31**, 208.
12. Johnston, J. *Amer. J. Syph.* 1951, **35**, 79.
13. Wilkinson, A. E. *Brit. J. vener. Dis.* 1952, **28**, 24.

Roiron [14] examined cultures from 1091 prostitutes; gonococci were grown from 44 and other neisseriæ from 89. Repeated cultures were performed on 65 prostitutes from whom gonococci had frequently been grown in the past; gonococci were isolated from 2 and other neisseriæ from 17 of these patients.

Attention has been drawn to organisms of the mima group described by DeBord.[15] These are diplococci or coccobacilli when first isolated; but on subculture they show true bacillary forms, especially when grown in fluid media. They are predominantly gram-negative, but some organisms in a smear may partly or completely retain the gram stain. They grow well on unenriched media, and *M. polymorpha* and its oxydase-positive variant do not ferment the common carbohydrates. Those studied by DeBord were isolated from the vagina and conjunctiva, but they are probably fairly widely distributed; Deacon [16] examined strains obtained from war wounds, brain tissue after head injury, a chancroidal lesion, and the urethra.

The resemblance of *M. polymorpha* (particularly the oxydase-positive type) to the gonococcus makes its recognition especially important. It can be differentiated from the gonococcus by its colonial and microscopical appearance and by fermentation reactions. Cary et al.[17] have described a slide agglutination test to aid in its identification.

Ino et al.[18] reported the isolation of *M. polymorpha* from 2 cases of urethritis which failed to respond to treatment with penicillin. Svihus et al.[19] investigated 42 men with urethritis at a United States Naval station in Naples. Gonoccoci were cultured from 11 of these men; in-vitro tests by a disc method showed that these strains were sensitive to penicillin, and the patients responded to treatment with 1,200,000 units of benzathine penicillin G and 600,000 units of procaine penicillin G in aqueous suspension. Mima was grown from 22 patients, and 18 of these strains were resistant to penicillin in vitro; treatment with the same dosage of penicillin was ineffective, but the patients subsequently responded to one or another of the broad-spectrum antibiotics. Ino et al. apparently feel that these organisms were responsible for the urethritis in the patients studied; but further evidence of pathogenicity will be required before this view can be accepted. Gangarosa and Cary [20] have questioned the validity of recent reports of gonococci resistant to penicillin, on the ground that infection with organisms of the mima group were not excluded. This criticism cannot be applied to the report of the Medical Research Council's Working Party,[21] in which the gonococci examined were identified by accepted bacteriological criteria. This survey yielded further evidence that strains of gonococci isolated from patients in whom treatment with penicillin has been unsuccessful are often relatively insensitive to penicillin.

Much has still to be learnt about the mima group of organisms. Work on them so far has shown their importance to the bacteriologist who is called on to examine material from the urogenital tract and emphasises the need for careful identification of organisms suspected of being gonococci.

14. Roiron, V. *Rev. du Practicien*, 1957, **7**, 2513.
15. DeBord, G. G. *Iowa St. Coll. J. Sci.* 1942, **16**, 471.
16. Deacon, W. E. *J. Bact.* 1945, **49**, 511.
17. Cary, S. G., Lindberg, R. B., Faber, J. E. *ibid.* 1958, **75**, 43.
18. Ino, J., Neugebauer, D. L., Lucas, R. N. *Amer. J. clin. Path.* 1959, **32**, 364.
19. Svihus, R. H., Lucero, E. M., Mikolajczyk, R. J., Carter, E. E. *J. Amer. med. Ass.* 1961, **177**, 121.
20. Gangarosa, E. J., Cary, S. G. *ibid.* 1960, **173**, 1808.
21. Report by Medical Research Council Working Party, *Lancet*, July 29, 1961, 226.

LUBRICATION OF JOINTS

THE causes of osteoarthritis are still obscure, but there are good grounds for believing that a failure of the normal joint-lubricating mechanism ranks high among them. It is disconcerting, therefore, to realise, when considering the possibility of preventing this disease, that our knowledge of how that mechanism operates even in healthy joints is still far from complete.

The viscid nature of synovial fluid, and the slippery sensation it imparts to surfaces coated with it, have for centuries encouraged the assumption that its primary role is facilitation of joint movement. But former views of its origin by exudation from the bone-marrow, or by secretion from fat pads, are no longer tenable. It is now generally held to be derived, by dialysis, from plasma, and to be enriched with polysaccharides (notably hyaluronic acid) synthesised by the cells of the synovial membrane.

Barnett, Davies, and MacConaill, in a new book,[1] suggest that the fluid acts as the liquid component of a " fluid film " system. This is one in which a lubricant coats the moving surfaces with a thin layer which remains an integral part of them, while the actual movement occurs between the molecules of another portion of the fluid, interposed between the two surfaces. (The effect can be compared to that produced by pressing the palm of the hand upon a pack of playing-cards lying on a table. Sliding movements of the hand across the table top are facilitated by the cards, because each of them moves slightly upon that beneath it, except those at the top and bottom of the pack, which remain fixed.)

Objections have been raised to this concept, on the grounds that such " fluid films " can persist, and can act effectively, only in situations where the movement of the bearing surfaces is relatively rapid, consistent in direction, and continuous. Such conditions, it has been said, often appertain in machinery, as in a propeller shaft spinning within its casing: but not in anatomical joints, the slow and alternating motion of which would squeeze away any fluid from between the articular surfaces. Charnley [2] has therefore postulated a system of " boundary lubrication ". A boundary lubricant is one which will operate " between solid surfaces separated by a fluid film which is too thin to behave as a fluid . . . it reduces friction by entering into physico-chemical combination with the surfaces, and diminishes the free molecular attraction which may seize the surfaces together ". Articular cartilage may be regarded in this context as a spongy network with the lubricating polysaccharide molecules trapped in its interstices.

Those who defend the " fluid film " hypothesis may reply to their critics that synovial fluid and articular cartilage have characteristics which make possible the persistence of a film in a joint under conditions which would rupture it in a machine. For synovial fluid is a " disperse solution " of long-chain molecules and behaves differently from pure oils composed of relatively simple molecules. Its viscosity rises as the rate at which a shearing strain applied to it falls: thus during a slow movement it resembles a very thick oil, and forms tenacious films which do not easily break down.

These conflicting opinions may yet be reconciled by the recognition of some special lubricating pattern, with no exact analogy in engineering. Barnett et al., writing of such

1. Synovial Joints. By C. H. BARNETT, D. V. DAVIES, and M. A. MACCONAILL. London: Longmans, Green & Co. 1961. Pp. 304. 50*s*.
2. Charnley, J. *Lancet*, 1961, i, 1129.

a pattern, point out that evidence exists that intermolecular sliding movement can occur in films which are only a few molecules thick, and much thinner than those to which the original fluid-film hypothesis applied. Articular cartilage can be shown to imbibe and expel synovial fluid as the pressure on it varies. If such a release of even small amounts of fluid took place during joint movement, a "weeping" system,[3] would result; and this might explain many anomalies in our present ideas.

USE OF AMBULANCES

ONE of the duties laid on local health authorities by the National Health Service Act of 1946 was to "make provision for securing that ambulances and other means of transport are available where necessary, for the conveyance of persons suffering from illness, mental defectiveness or expectant or nursing mothers from places in their area to places in or outside their area". Each year some 15 million patients are carried by the ambulance services, and on the whole these have worked very efficiently.

Suggestions for a change in the arrangements have been made from time to time; and the latest comes from the chairman of the Birmingham health committee. Because, it is alleged, doctors and hospital staff are ordering ambulances for patients "in the same way as you order a taxi" and "making it difficult to attend emergencies quickly", he has appealed to all parties not to ask for ambulances "unless they were necessary", and he has expressed his personal belief that the Act should be amended so as to make the regional hospital boards responsible.[4] In other areas, however, we have found that a less serious view is taken of the abuses of the service: indeed some of those questioned think that these are lessening rather than increasing. It is encouraging to note the frequent comment that practitioners do not misuse the service—though patients and inexperienced junior hospital staffs occasionally err.

For instance, unscrupulous persons wanting to be admitted to hospital have been known to dial 999 and say that they were seriously ill. One man, who claimed at 2 A.M. that he had active pulmonary tuberculosis, was in fact a morphine addict with no chest lesion. Several patients have been taken by ambulance to the hospital for outpatient treatment but have preferred to walk home so as to do some shopping or visit sports meetings. One patient was told to walk five miles a day but insisted on being transported to the hospital grounds where he could take this exercise. Another type of case is that of the man who possessed a bicycle and who "required transport" to the hospital physiotherapy room for exercises on a fixed bicycle.

Economy can be achieved by asking hospital authorities and family doctors to give notice of their transport requirements as long as possible in advance. Hospitals may be able to arrange that patients from the same localities, or neighbouring ones, have appointments around the same time, while practitioners can, so far as possible, arrange appointments for patients at the nearest hospital. Rail transport should often be preferred for long-distance cases; and, needless to say, the ambulance service should not be asked to take people on holiday or to places of recreation.

If a patient needs an ambulance on medical grounds, the local authority must see that he has one—subject to the final decision of the medical officer of health of the ambulance authority. As a certificate from a general practitioner virtually compels an authority to provide an ambulance, special responsibility rests on practitioners to satisfy themselves that the patient cannot suitably travel by other means. Often the need for transport is obvious; but sometimes such factors as the age of the patient, the availability of public transport, and the nature and duration of the treatment provided at the hospital have to be taken into consideration. General rules are: (1) accident and emergency calls are answered without question, whatever their source; (2) after a practitioner has authorised the first journey to an outpatient department, further journeys must be authorised by the hospital (in other words, authorisation should originate from the source where treatment is being given); and (3) discharges or interhospital transfers have to be authorised by the hospital which the patient is leaving. A welcome change has taken place in long-distance work now that the local authority can get British Railways to provide a special compartment for a stretcher case. Travel by rail is usually more comfortable than travel by road; the journey takes less time and is far less expensive. The kindness and efficiency of railway staff have been proved time and time again.

It is important alike to the ambulance and to the hospital authorities that they should make mutually satisfactory arrangements to ensure that the ambulances are used to full advantage. This is best done by day-to-day contact between the operational ambulance staff and the hospital executives responsible for placing orders for patients' journeys.

MUCORMYCOSIS IN BURNS

BACTERIAL infection of burns remains very common despite all the antibiotics; for, although infection with the once-dreaded *Streptococcus pyogenes* can usually be prevented or eliminated, other organisms—especially *Staphylococcus aureus*, *Pseudomonas pyocyanea*, and various coliform bacilli—are still a danger and a challenge. Most patients with extensive burns can now be brought safely through the shock phase by fluid therapy, but septicæmia or pneumonia still quite often develops from bacteria which have colonised the burn—and many of these patients die. Like other patients treated with broad-spectrum antibiotics, some burned patients (particularly children) develop moniliasis of the pharynx and alimentary tract, which sometimes causes or contributes to death. Fortunately the burned tissues are not readily infected by yeasts and fungi; but two cases of fatal fungal infection of burns have been reported by Rabin et al.[1]

The patients were extensively burned and were already seriously ill with pyrexia and attacks of hyperpyrexia from septicæmia before the infection was manifest clinically. They had been treated with a variety of antibiotics: penicillin, novobiocin, chloramphenicol, and colistine sulphate in one case; and penicillin, streptomycin, and tetracyclines in the other. Then, in the second and third weeks after burning, areas of dry black gangrene appeared on the burned faces and extended into the nose, lips, and maxilla, producing widespread destruction of the face and nasal cavity. The description is not unlike that of the disorder known to previous generations as *cancrum oris*. Fungal infection was not suspected clinically; but postmortem histological

3. McCutchen, C. W. *Nature, Lond.* 1959, **184**, 1284.
4. *Birmingham Post*, Aug. 24, 1961.

1. Rabin, E. R., Lundberg, G. D., Mitchell, E. T. *New Engl. J. Med.* 1961, **264**, 1286.

examination revealed broad, branching, non-septate hyphæ in sections of the necrotic tissue, and the infection, on morphological grounds, was thought to be mucormycosis. Direct extension to the meninges and visceral dissemination were also found. Disseminated mucormycosis in a burned patient without involvement of the face had previously been reported by Baker.[2]

Mucor is one of the phycomycetes characterised by a non-septate mycelium that is without cross-walls, and the hyphæ are much broader than those of other infecting fungi. Local infection has been reported in the fingernails of citrus pickers, but cerebral and generalised forms have been observed.

Mucormycosis has attracted attention in the United States.[2–5] It is hardly known in this country, where, however, Symmers [6] has drawn attention to a variety of visceral fungal diseases including mucormycosis. In many of the cases of cerebral or generalised disease reported from the U.S.A. the patients were already ill with leukæmia or other debilitating disease, and others had diabetes mellitus.[7] Administration of antibiotics, steroids, or anti-metabolites and radiation therapy seem to predispose to invasion, particularly in the debilitated; and possibly the mucor invasion in the two cases of burns described by Rabin et al. was promoted by the necessary use of several antibiotics for the treatment of septicæmia due to *Staph. aureus* and *Ps. pyocyanea*.

MORTALITY AND MORBIDITY AND THE ATMOSPHERE

J. S. Haldane, whose centenary year this is, would surely have approved of the present interest in the effects on life and health of the physical and chemical properties of the air we breathe; for this was a theme which recurs in some of his own most memorable work. But, whereas Haldane was often concerned with problems which by their nature were amenable to solution by direct experiment (even if experimenter and subject had sometimes to be one and the same person), those which are of current concern can only be approached more indirectly. What are the effects—immediate and remote—of atmospheric pollution on the health of exposed populations? What components —climatic and man-made—in the atmospheric environment produce these several effects? These questions, as Martin [8] points out, are customarily tackled by correlation analysis—an approach which has the inherent defect that it can never, alone, prove a causal relation. True, no very subtle statistical reasoning is needed to conclude that the abrupt rise in the number of deaths in Greater London in the second week of December, 1952, was a direct consequence of the smog that enveloped the area for four consecutive days. But even where the sequence of events is so dramatically obvious, interpretation may still be difficult. It has, for example, been plausibly suggested that smog on this scale causes a temporary rise in mortality because of its capacity to administer the coup-de-grâce to patients already seriously ill. Certainly, mortality commonly drops to an unusually low level in the period immediately after the rise.[9] It appears, too, that the injuriousness of atmospheric pollution varies with the temperature. Boyd [10] found that in London the effect of fog on mortality was most serious where the atmospheric temperature was at or below freezing-point. In rural East Anglia, on the other hand, fog per se (i.e., decreased visibility) did not significantly influence mortality even at freezing temperatures. This points to a synergic effect between low temperatures and, presumably, the chemical components which are to be found in a London " particular " but which are absent from the atmosphere of rural areas.

If polluted air can influence mortality, then we should expect that it would also affect morbidity. The demands on the Emergency Bed Service during and after the Great Fog of London were described by Abercrombie.[11] Similar, though smaller, effects of short-term variations in pollution on hospital admission-rates have been detected even in years when smog was not unusually prevalent. Apparently as much as 10% of the daily variation in total hospital admissions in the Greater London area in winter is related to the amount of black suspended matter in the atmosphere; but, curiously enough, the variation in admissions from respiratory conditions which is similarly related is no greater than the variation in total admissions. This apparent anomaly, besides raising some interesting speculations (is hernia more likely to strangulate if there is smog about?), suggests that the influence of pollution on health may be more penetrating than we customarily think.

Applying a slightly different technique of analysis to the monthly applications for admission because of respiratory disease to the Emergency Bed Service in Greater London throughout the year, Holland et al.[12] found that at ages over 15 years both atmospheric pollution and atmospheric temperature exert a significant influence independently one of the other. Four other meteorological variables (humidity, rainfall, barometric pressure, and sun-hours) seemed to have no independent association with hospital admissions. An effect of temperature on the incidence of acute respiratory illness was also found among R.A.F. personnel at four stations.

Ill health not serious enough to require admission to hospital also seems to vary according to the condition of the atmosphere. For example, the day-to-day condition of chronic bronchitics has been shown to be related to a daily index of atmospheric pollution.[13] (Asthmatics in Los Angeles, by contrast, were not more liable to attacks when the level of atmospheric oxidants rose.[14] It might be instructive to repeat this work in this country, in view of the known differences between the chemical composition of pollution in Los Angeles [15] and in our own large cities.) Fairbairn and Reid,[16] studying postmen—an occupational group within which conditions of work and other social factors associated with employment might be expected to be relatively uniform throughout the country—concluded that these were the more subject to chronic bronchitis, and the more disabled thereby, the greater the amount of fog which they encountered in their work.

2. Baker, R. D. *Amer. J. Path.* 1956, **32**, 287.
3. McBride, R. A., Corson, J. M., Dammin, G. J. *Amer. J. Med.* 1960, **28**, 832.
4. Hutter, R. V. P. *Cancer*, 1959, **12**, 330.
5. Smith, H. W., Kirchner, J. A. *Arch. Otolaryng.* 1958, **68**, 715.
6. Symmers, W. St. C. *in* Fungus Diseases and their Treatment (edited by R. W. Riddell); p. 25. London, 1958.
7. Berk, M., Fink, G. I., Uyeda, C. T. *J. Amer. med. Ass.* 1961, **177**, 511.
8. Martin, A. E. *Mon. Bull. Min. Hlth Lab. Serv.* 1961, **20**, 42.
9. Martin, A. E., Bradley, W. H. *ibid.* 1960, **19**, 56.
10. Boyd, J. T. *Brit. J. prev. soc. Med.* 1960, **14**, 123.
11. Abercrombie, G. F. *Lancet*, 1953, i, 234.
12. Holland, W. W., Spicer, C. C., Wilson, J. M. G. *ibid.* Aug. 12, 1961, p. 338.
13. Waller, R. E., Lawther, P. J. *Brit. med. J.* 1957, ii, 1473.
14. Schoethlin, C. E., Landau, E. *Publ. Hlth Rep., Wash.* 1961, **76**, 545.
15. Fair, G. M. *J. R. Soc. Hlth*, 1959, **79**, 524.
16. Fairbairn, A. S., Reid, D. D. *Brit. J. prev. soc. Med.* 1958, **10**, 94.

Special Articles

A TEAM SYSTEM IN A MENTAL HOSPITAL

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FOR general hospitals in this country the team (or firm) system has always been an accepted practice.

A consultant has a number of beds of his own, sees his own outpatients on a given day, and when he does a domiciliary visit admits the patient to one of his own beds. When the patient is discharged the consultant sees him again in outpatients. In other words it is clearly understood that the consultant has a personal and continuing responsibility for any patient that is referred to him. To assist him in his work he has various grades of junior staff. He always has a house-physician who, under his direction, carries out detailed treatment. Sometimes he may have a registrar or a senior registrar as a member of his team or firm. The consultant does ward rounds with his junior doctors not only to supervise the treatment of his patients, but to teach the younger members of his firm.

For many years, however, the practice in mental hospitals has been different.

The patient is often referred to a psychiatric clinic rather than to a named consultant. If the patient is to have outpatient treatment, he will probably continue to be treated by the doctor who originally saw him. But if the patient is admitted to hospital he will probably find himself under the care of another doctor, and he has to go through the whole business of once again telling his story. If he is transferred to a different type of ward, he will find himself under yet another doctor; and finally, when he leaves hospital, the letter to his general practitioner was, until lately, often signed by yet another person—the medical superintendent.

This procedure strikes at the very root of personal medicine and has often led to an impersonal and indifferent approach to patients and a standard of care far below the ideal. It is particularly regrettable in psychiatry where the relation between patient and doctor is all-important. Its origin can be found in the history of the mental-health services.

Before 1948 there was really only one consultant in each mental hospital—the medical superintendent. By law he was legally responsible for the care and treatment of every patient in his institution, but as his hospital might have over 1000 beds, it was impossible for him to supervise in detail the treatment of all " his " patients. He was also responsible for running the whole hospital, and too often he became a man overburdened with details of administration. To help him, assistant medical officers were appointed. Often one senior assistant was put in charge of the male side and another in charge of the female side of the hospital. These two sections were to all intents and purposes divided by an iron curtain.

In the early days little outpatient work was done. But in time the medical superintendent and one or more of his assistants began to hold weekly clinics in the local general hospital. If the medical superintendent advised admission, the patient would be treated either by the doctor in charge of the male side or the doctor in charge of the female side. The medical superintendent probably never saw the patient again; but, because he was legally charged with the care of this patient, he might arbitrarily interfere from time to time in the treatment given by his assistant. He alone recommended such things as leave or discharge, and he signed all letters to general practitioners.

When the health service was started in 1948 consultant psychiatrists were appointed to mental hospitals. These consultants were paid at the same rate as the medical superintendent and rightly considered that they should be given absolute responsibility for their patients. But the medical superintendent remained legally responsible for all the patients in the hospital. This has led to considerable friction and even bitterness. Under the new Mental Health Act the medical superintendent is no longer statutorily responsible for the clinical treatment of any patient other than those personally under his care.

OUR SOLUTION

In August, 1959, at this hospital we decided to anticipate the new Act and set up a system whereby each consultant had full clinical responsibility for his patients. For several years an attempt had been made to increase consultant responsibility by allotting every new patient to a consultant by name on admission. But this had not proved satisfactory; for consultants shared admission wards, long-stay wards, and junior doctors, and unless a patient was discharged in a short time he tended to become " lost ".

It was now decided to divide the hospital into three independent and functionally autonomous units, each with 300 beds. The division was made, not in the old vertical way—i.e., male on one side and female on the other—but horizontally, so that each unit now has male and female patients. Furthermore each unit can cater for both acute and long-stay patients. As it happened, the upgrading of the old-fashioned wards had only just begun, and this made our task easier, because as each ward is due for upgrading we are able to design it architecturally to fit in to the team system.

Each team now has a mixed villa—that is to say, a separate ward which takes about 15 male and 15 female patients. The primary object of the villa is to have in it the very best type of long-stay patient, so that admission cases which need no nursing observation can also be accommodated and treated there. The overcrowding in the hospital makes it impossible to use these villas solely for new admissions.

Secondly, each team has a male and female admission ward for acute cases needing full nursing supervision. Though these wards are one nursing unit, they are being redesigned so that elderly patients and young acute psychotics can be separated.

The central infirmary or sick wards were abolished: each consultant is responsible for his own physically ill patients, and these are nursed in a section of the admission wards. At present we have some difficulty in nursing the elderly sick in these wards, but when the upgrading is complete this problem, we are confident, will disappear.

Each team also has its own long-stay wards to which it can transfer suitable patients.

No patient is admitted without the consent of a consultant psychiatrist, who frequently visits him in his home or sees him in outpatients. Once admitted, the patient is under the care of a team, and the consultant in charge of that team is responsible for him throughout his stay in hospital and also for his aftercare when he returns to the community.

Each team has a weekly outpatient session. The general practitioners have been notified of the days on which each team sees outpatients and the name of the consultant in charge. This means that the general practitioner can choose which consultant shall see his patient.

He can also have the consultant of his choice for a domiciliary visit. (Under the old system, very often all domiciliary requests were sent to the medical superintendent who arbitrarily decided whether he made the visit himself or delegated it to one of the other doctors.) Each team is " on take " for a week at a time. The senior psychiatrist " on call " is responsible for all emergencies in the catchment area of the hospital, and these patients are admitted to his unit and treated in it.

STAFF

Medical

We consider that ideally a team serving three hundred psychiatric beds, of which forty are admission beds, should have 2 consultants, 1 registrar, 1 junior hospital medical officer, 1 senior house-officer, and 1 general-practitioner clinical assistant. The three junior grades would allow a young doctor to have 3–4 years' training and experience in psychiatry with the prospect of yearly promotion, and by the end he should have his diploma in psychological medicine as well as a thorough grounding in the essentials of psychiatry.

In a hospital like ours it is clearly unrealistic to hope to have three senior registrars (one for each of our teams). We also find that some of the junior staff wish to spend only a year with us, to gain psychiatric experience before entering general practice. The general-practitioner clinical assistants in each of our teams, who come for two sessions a week, are a beneficial link with the general-practitioner service.

We have not as yet reached the ideal establishment but we shall press for it. At present our teams are:

Team 1	*Team 2*	*Team 3*
1 consultant	1 consultant	1 consultant (also medical superintendent)
1 S.H.M.O.	1 S.H.M.O. (with special allowance)	1 consultant (also i/c E.G.G. dept.)
2 J.H.M.O.	1 registrar	1 registrar
1 general practitioner	1 J.H.M.O.	1 J.H.M.O.
	1 general practitioner	1 general practitioner

Nursing

Each team has an assistant chief male nurse and an assistant matron, responsible to the matron and chief male nurse respectively for the nursing of the patients on that team. There is much to be said for each team having a permanent nursing staff at all levels, but shortage makes this impossible.

Other staff

Each team has its own hospital social worker, mental-welfare officers, occupational therapists, and a chaplain. We feel that the social worker should shoulder the more difficult case-work and social problems of the patient both in the hospital and outside in the community. As the local authority expands its services we hope that we shall have three mental-welfare officers on each team, one of whom will spend a large part of his or her time at the hospital and so gradually benefit from close contact with the psychiatrists and in due course become as experienced in social case-work as his hospital colleague. The hospital social workers also take a large part in organising the social and recreational groups on their teams, always working with the occupational and nursing staffs. We are able to have a chaplain for each team because the local vicar, who is part-time chaplain to the hospital, has two curates.

ADMINISTRATION

Each team has a life of its own, organises its own social and recreational activities, and is an independent psychiatric unit able to deal with all types of psychiatric in-patients and outpatients. All members of the team, down to student-nurse level, meet weekly for discussions or clinical case-conferences geared to the needs of the nurses. New ideas and suggestions to increase efficiency are brought forward; and, if they do not need any radical change in ward usage, mass movement of patients, or change of hospital policy, they are put into practice without further reference to anyone.

As the teams developed they became so independent in their life and thinking, that the chief male nurse, matron, and administrative officers found themselves dealing with three separate medical superintendents all clamouring for immediate recognition of their demands. This led to tension, anxiety, and confusion; and the chief male nurse and matron felt that they were being by-passed and not informed on matters which concerned them. Now, however, a senior officers' committee has been formed, composed of the hospital secretary, group secretary, consultants, matron and chief male nurse, with the medical superintendent as chairman, and major changes of policy must not be put into operation until approved by this committee. A bulletin of its activities is circulated to all members of the staff. So that all have an opportunity of expressing their views, it considers all such matters as refurnishing or upgrading of wards, though it is assumed that details have already been discussed at ward and team level.

The medical staff meets twice a month, and the senior medical staff once a month, under the chairmanship of the medical superintendent. The hospital also has a medical advisory committee which meets every two months; but, as consultants in other specialties attached to the hospital sit on this committeee, it is found in practice that the senior officers' committee and the medical staff committee are the effective government of the hospital.

THE MEDICAL SUPERINTENDENT

Each team has freedom to arrange the clinical care of its patients, and the medical superintendent no longer signs letters for other doctors, interviews patients before discharge, does clinical rounds on other than his own wards, or knows anything about patients not under his immediate care. But his role, though new, is still essential. He is a clinician, doing the same work as his consultant colleagues, and his administrative duties are an addition to his clinical work. But these administrative duties are still vital, and I believe that the efficiency of the hospital would suffer if he were replaced by an elected " rotating " chairman of a medical staff committee.

The medical superintendent's functions now fall under two headings:

Within the hospital he remains chief officer in the sense that he is directly responsible to the committee for the administrative efficiency of the medical services. He is responsible for coordinating the work of the chief male nurse, the matron, the medical staff, and all the auxilliary medical departments. Though he has no right to interfere clinically, it is his job to be aware, in a general way, of all that goes on in the hospital. He should be a coordinator, catalyst, stimulator and, if you like, group psychotherapist. He should not be the originator of all new ideas, but he should provide a background of encouragement, so that all levels of staff should feel that their views will be given a sympathetic hearing.

Because he is appointed from outside and not elected from within, and because he is responsible only to the committee,

he should be able to take an impartial and independent view of clashes between departments or staff members. His power to veto harmful suggestions should be a steadying influence throughout the hospital.

Again, because he is responsible to the committee, he has the right to attend all committee meetings, and to advise on any problem; and his advice can only be ignored after due and proper consideration by the committee. In a word, his views carry more weight than the views of any rotating chairman or medical advisory committee. He is not above the group secretary but equal with him. As permanent officers the two can build up a strong relationship with their committee and a useful relationship with each other. They should work in harmony and should share their ideas and views; for they have common problems which must be solved in a way acceptable both to administration and clinical medicine.

Outside the hospital the medical superintendent, again because of his permanency, is recognised as its contact point. He is the ideal person to deal with the medical officer of health and all other agencies concerned with the care of the mentally ill. His presence means that any patient or general practitioner with complaints or grumbles about medical care has direct access to a doctor, whereas a lay administrator would have to seek medical opinion. According to the nature of the complaint, the medical superintendent may refer it to the consultant in charge or, if it is due to interdepartmental troubles, he may initiate an inquiry. He is also in direct contact with the senior administrative medical officer of the regional board and because of his knowledge of the whole hospital and its problems over a period of time can give a more reasoned opinion than a rotating chairman.

It is almost impossible to define fully the role of a medical superintendent. Many of those who wish to see him done away with are unaware of the intangible problems that he has to solve. His office should not be swept away without careful thought.

CONCLUSIONS

Our practice is far from perfect and what we have done may not be applicable everywhere; but I believe that we have set up in an ordinary provincial mental hospital a system which allows us to enjoy the benefits of the general hospital medical firms.

Our system of communication within the hospital is not too cumbersome, yet gives everyone an opportunity of knowing what is going on. Everyone has some say in how things are run, yet there is sufficient control to prevent anarchy.

Junior medical staff are immediately initiated into the full life of a psychiatric hospital, and gain experience in all types of psychiatry. From their first day to their last day they are given supervision and instruction in outpatient clinics, at the bedside, and at formal clinical conferences and tutorials.

This system is a product of sharing ideas. It could not have been started without the willing and constructive participation of the medical, nursing, and administrative staff. The initial difficulties were enormous, because it was a breakaway from entrenched tradition. I should like, therefore, to thank all members of the staff (perhaps especially our energetic junior medical staff who at times prodded their seniors) for their cooperation and at times forbearance when we did not know quite where we were going. In particular I want to mention Miss N. S. Brymer, the matron, and Mr. R. R. J. Hard, the chief male nurse. I must thank Dr. C. E. H. Turner, consultant psychiatrist and deputy medical superintendent, who nobly urged the splitting of the hospital and gave so much thought to its details. I should also like to thank Mr. M. D. Groves, the group secretary, who suggested the senior officers' committee as a solution to proper coordination and gave valuable administrative support and advice.

WIRELESS CONTROL OF BLOOD DELIVERY

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THE distribution of blood to hospitals from the North London Blood Transfusion Centre has been based on an arbitrary quota for each hospital, depending, of course, on size and activity. Some hospitals are supplied weekly and some twice a week by refrigerated vans of our own design. When a hospital needed blood of any group or rhesus type before the next delivery was due, the hospital sent its own transport to the centre. This method involved a delay, which varied of course according to the distance from hospital to centre, and the ease with which the hospital could secure a vehicle.

Having in mind the use of two radio-controlled vans holding emergency supplies in insulated boxes (with ice inserts), we asked Pye Telecommunications Ltd. about the cost of transmitting and receiving sets, and Spurling Motors Ltd. about the vehicles. Two drivers only would be needed to run the service since a replacement for holidays and sickness could come from the existing establishment. After the initial outlay for equipment, it seemed that the running costs of the radio-controlled service would approximately equal the cost to the regional hospital board of sending vehicles to the centre from hospitals. The treasurer's department of the regional board were not prepared to agree entirely with this point, but they did not consider that their calculations would be to the disadvantage of the scheme.

The first step was an exercise on paper without equipment, using two hypothetical vans moving out from two base points and delivering blood at each telephone request. When the records were examined after three months it was evident that a saving in time had been made on each call.

The next move was to ask Pye Telecommunications whether the scheme was feasible. Equipment was loaned free of charge for a trial test of three months, and the mobile equipment was fitted to one of the reserve refrigerated delivery vans. A test was carried out from one of the offices at the centre, using a land-line hired between the centre and Pye's transmitting aerial at Hampstead Heath.

It soon became evident that, with the exception of Bedford General Hospital, a distance of 45 miles, it was possible to reach our vans operating north and west of London at most points, though blank spots were found where transmission was poor or nil. The drivers soon got to know these areas. The driver, after delivering blood to Bedford General Hospital, would telephone by land-line to the centre to ask for any further instructions, and if there were none, he would proceed south again without delay until he came into operational range, when he would report by radiotelephone.

As a result of the three months' trial it was decided to ask the regional board to sanction such a service, and this was done.

Operating the Radio-controlled Vans

The fixed transmitter is a PTC 2702 25-watt transmitter/receiver with vertical dipole aerial and operates on a frequency of 166·1 mc/s. It is situated on top of Brockley Hill, 460 feet above sea level with a sharp fall away to the north giving a good "take off". The aerial is 73 ft. high and is on top of the Convalescent Block of the Royal National Orthopædic Hospital. Two control panels (PTC 411) in parallel are installed at the

North London Blood Transfusion Centre, with remote control switches, and connected to the transmitter by G.P.O. land-line. The mobile stations are two 8 h.p. 1/4-ton Morris Commercial vans equipped with PTC 2202/v Ranger mobile sets on 170·9 mc/s with a vertical quarter-wave whip aerial. All the equipment was supplied by Pye Telecommunications Ltd. and the aerial by R.T. Masts Ltd.

The initial cost of the vehicles and equipment was £1874 and the running costs were estimated at £2238 per annum.

The following stocks are carried by each van: 12 group-O blood, 12 group A, 4 group B, 2 group AB, 5 group O rhesus-negative, 5 group A rhesus-negative, 2 group B rhesus-negative, 2 group O rhesus-negative, and 2 group A rhesus-negative fresh blood for exchange transfusion in infants, 20 plasma, and distilled water.

At 9.30 A.M. the two vans set out for their base rendezvous, "Alpha" to St. Albans City Hospital and "Bravo" to Mount Vernon Hospital. Requests for blood often arrive at the centre before 9.30 A.M. in which case the appropriate van will make directly for the hospital, carrying the extra supplies. Before setting out, the equipment is tested by speaking to the transmitting station at the centre. To safeguard against accidental breakdown of equipment each driver calls the centre every hour. If he failed to contact the centre by radio he would immediately report by telephone. The vans return to the centre at 5.30 P.M. After this time the system of emergency night banks in the region comes into force until 9 A.M. the following morning. All drivers are trained in the use of these vans and drive them in daily rotation to ensure continuing efficiency.

This service has proved very satisfactory and has fulfilled its original intention.

Public Health

POLIOMYELITIS AND PHOTOPERIODICITY

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THROUGHOUT a great part of the world poliomyelitis shows regular periodicity. Outside the tropics, in the Northern as well as the Southern Hemisphere, the epidemic increase occurs in the same season. A lowest point towards the end of the winter (*interepidemic* stage) and a gradual beginning in early spring (*pre-epidemic* stage) are followed by a rise, culminating in late summer or autumn (*epidemic* stage), and a *postepidemic* fall in winter.

The present paper deals with the causes of this seasonal variation. For the purpose of my investigation I must restrict myself largely to the pre-epidemic stage; for during the epidemic stage the study of an exogenic factor would be complicated by various confusing factors—social and immunological as well as virological.

From the World Health Organisation's *Epidemiological Reports* I took the absolute monthly (or four-weekly) figures of 21 non-tropical countries in both hemispheres in 1952–56. The figures for the Northern Hemisphere show that the mean lowest points for the Netherlands, Western Germany, Greece, Italy, the U.S.A., Israel, and Japan were in March (in the third four-weekly period of the year); for Denmark, Norway and Canada they were in April; and for Sweden they were in March–May. In Spain the morbidity-rate remained very low throughout January, February, and March; in Finland, from January to April. Thus the totals for the interepidemic stages, even though they are small, demonstrate that in the Northern Hemisphere the annual pre-epidemic appearance of poliomyelitis usually comes immediately after the interepidemic lowest point in March or, less often, in April (fig. 1).[1]

Allowing for possible variations in these small numbers, the conclusion must be that all over the Northern Hemisphere outside the tropics the onset of the epidemic increase of poliomyelitis was well-nigh simultaneous.

In the Southern Hemisphere the number of poliomyelitis cases in all countries studied reached their peak in the first six months of the year, and fell to their lowest point in the second half. In all five countries—Argentina, Brazil, Chile, South Africa, and Australia—the mean lowest numbers were found in September or in the tenth four-weekly period of the year, and were therefore limited to a comparatively short period, as in the Northern Hemisphere. It follows that in the Southern Hemisphere, too, the onset of the epidemic increase of poliomyelitis was well-nigh simultaneous in all countries studied (fig. 2).[1]

The factor which primarily actuates this seasonal variation is unknown; but it is evidently bioclimatological —a function of the world's timepiece which can be recognised in the Northern and Southern Hemispheres by the seasonal variation of poliomyelitis. It cannot be thermal, for meteorological instruments have failed to furnish a clue. Severe epidemics have occurred in warm dry summers as well as in cold and wet ones. Meteorological conditions determined by temperature, humidity, rate of air movement, and rainfall are too variable to manifest themselves simultaneously and periodically in the rise and fall of the poliomyelitis-rate in a considerable part of the world. But another bioclimatological factor which must be mentioned is light. For it will be noticed that the seasonal increase of poliomyelitis in a great part of the world starts about the time that the days are beginning to get longer than the nights.

The epidemic course toward the end of the summer is also connected with daylight. It is not so synchronous all over the world as the pre-epidemic beginning; but the end usually comes in the late summer or autumn, when the difference between night and day is dwindling to zero. This period corresponds with the beginning of spring in the opposite hemisphere—i.e., the season in which poliomyelitis begins its epidemic course and the days are getting longer than the nights.

A third connection between the daylight period and poliomyelitis may be found in the tropical case-rates. Near the Equator there is little difference between the duration of night and day; and, if the seasonal factor which outside the tropics influences the seasonal variation of poliomyelitis is in any way associated with the daylight period, this seasonal phenomenon may be expected to be less in evidence near the Equator than in other parts of the world. I have therefore taken from the Geneva reports the four-weekly figures, mostly covering a period of eight years, for 13 countries situated near the Equator—namely, Ecuador, Colombia, Venezuela, and Cuba; Belgian Congo, Uganda, Kenya, and Tanganyika; Philippines, Indonesia, Singapore, Malaya, and Ceylon. In regions where there is very little difference between night and day, no definite seasonal variation can be established from these data (fig. 3).[2]

1. For full data see *Nederl. Tijdschr. Geneesk.* 1959, **103**, 851.
2. *ibid.* 1960, **104**, 2293.

DISCUSSION

The above facts turned my attention to the effect of light on physiological functions. Without going into the very extensive literature [3] I may say that experimental studies on the physiological significance of daylight have been made chiefly in connection with the sexual functions of birds, mammals, and fish (egg production, breeding season, &c.). The thickness and colour of pelts have been changed by artificial daylight. In some species of mice the numbers of eosinophil leucocytes in the blood can be changed by artificial light and darkness.

Cockroaches under normal conditions regularly show a burst of activity early in the night. This rhythm can be eliminated by exposing the animals to continuous illumination; but, if a cockroach thus rendered " arhythmic " is joined parabiotically to a normal cockroach, its activity is restored.[4]

Non-experimental evidence has less bearing on our problem; but I cannot refrain from mentioning the remarkable similarity between Stone's [5] and Shaw's [6] (Wisconsin) graphs of the seasonal variation of naturally occurring isoantibodies of cattle for the J substance and of man for the blood-groups A and B, and those for poliomyelitis in the Northern Hemisphere. In both the lowest point is in early spring, the peak in late summer. Osterhoff's [7] charts for the isoantibodies of cattle for the J substance in the Southern Hemisphere show the opposite picture.

Yeates, who experimented in this field—he changed the breeding season of sheep—concluded a paper on " daylight changes " [8] with these words:

" A striking feature of the natural light environment is the regularity with which the yearly changes are repeated in any one latitude. The annual light cycles for a particular locality are virtually identical, a condition which is far from being the case with other environmental factors, such as temperature, humidity, rainfall or pasturage."

Epidemiologists are ill prepared for the exceptional suggestion that the length of the daylight period might affect the intracellular association between man and his symbionts. Still it is to be hoped that Yeates's statement may arouse the interest of workers on the epidemiology of poliomyelitis—notably experimenters who might be in

3. Rowan, W. Proceedings of First International Photobiological Congress, Amsterdam, 1954; p. 46.
4. Harker, J. E. *Nature, London*, 1957, **173**, 689.
5. Stone, W. H. *J. Immunol.* 1956, **77**, 370.
6. Shaw, D. H., Stone, W. H. Proceedings of Sixth Congress of European Society of Hæmatology, Copenhagen, 1957; p. 726.
7. Osterhoff, D. Proceedings of Sixth International Conference in Blood-grouping, Munich, 1959; p. 96.
8. Yeates, N. T. M. *in* Progress in the Physiology of Farm Animals (edited by J. Hammond), London, 1954.

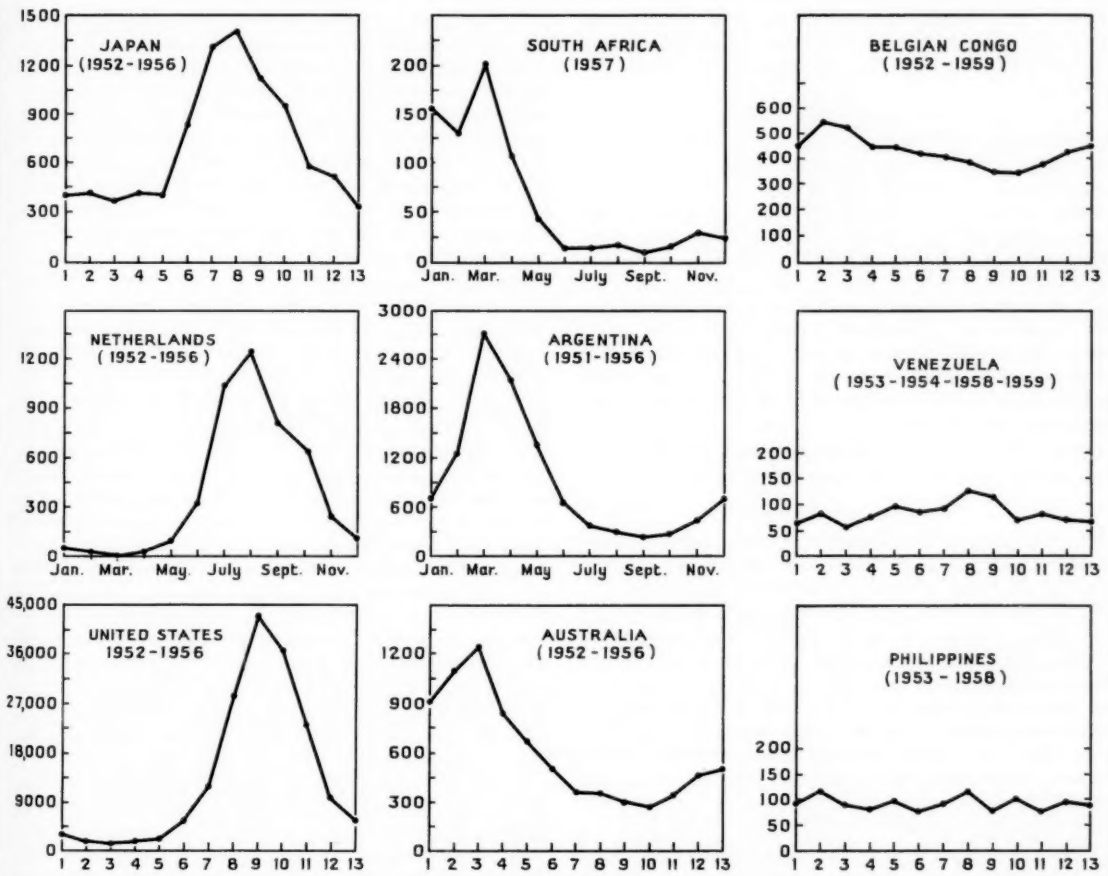

Fig. 1—Poliomyelitis Japan, Netherlands, United States monthly or 4-weekly periods absolute numbers.

Fig. 2—Poliomyelitis South Africa, Argentina, Australia monthly or 4-weekly periods absolute numbers.

Fig. 3—Poliomyelitis Belgian Congo, Venezuela, Philippines 4-weekly periods absolute numbers.

a position to study the effect of different types and quanta of light on animals infected with poliomyelitis virus, and on the culture of this virus.

SUMMARY

A worldwide bioclimatological factor may be responsible for the synchronous seasonal variation of poliomyelitis in Northern and Southern Hemispheres.

The hypothesis that daylight affects the symbiosis of man and poliomyelitis virus is supported by data on poliomyelitis-rates in tropical countries where no seasonal variation of the disease is seen.

Points of View

RECRUITMENT AND TRAINING OF MENTAL NURSES

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IN hospitals for the mentally ill and the subnormal, there is a severe shortage of trained nurses; and, except in a few favoured hospitals, most of the recruits for training are coming from other countries. Though some of them are very good indeed, their education level is sometimes poor; and by no means all those who qualify wish to take permanent senior posts in this country or are suitable for them.

This is only to be expected in view of the very low standard of pay and working conditions as compared with other jobs. For example, what girl would want to be a mental nurse, working a 44-hour week with 4 weeks holiday a year, if she could be a teacher working not much more than half that number of hours, with three times as much holiday, in a less exacting job, at higher pay? Yet the course of training for mental nurses is no less demanding and no shorter than a teachers' course, and requires an educational standard not very much lower. The student nurse may also compare his or her lot unfavourably with that of industrial workers, whose starting-wage is much higher with better conditions and much less responsibility.

In a word, the course of mental-nurse training is too long and too difficult for the kind of recruit we can get.

THE PRESENT SYSTEM

In its efforts to improve standards, the General Nursing Council has imposed on the mental hospitals a system of training, modelled on that of the general nurse, which is very largely irrelevant. In our hospitals there is in fact very little "nursing" as the G.N.C. understands the word. The actual "nursing" procedures which our nurses need to know are simple and can be very quickly learnt; for most of the work is training, teaching, rehabilitation, restoration of morale, and protecting the patients from harm. Of course we need some generally trained nurses, particularly where there are severely subnormal patients in cot and chair, or disturbed senile patients; but these need not be a high proportion of the total.

Unfortunately, in trying to be "nurses" in the G.N.C. sense, mental nurses have now stripped themselves of most of the interesting and pleasant and rewarding jobs in the mental and mental-deficiency hospitals.

These jobs are done largely by specialists such as physiotherapists, occupational therapists, psychiatric social workers, remedial gymnasts, and workshop managers. If the present tendency goes on, mental nurses will be little more than glorified charwomen. Even now they are regarded as persons engaged to do the unpleasant tasks—as persons whose function it is to act as custodians and feeders and cleaners-up of the patient until he can be handed over to some lady in a white coat or green overall to be trained or rehabilitated; and the mental nurse sweats it out in the ward until 8 P.M., and takes her turn of night duty, while the lady in the green overall—who has not got her hands dirty all day—trips off daintily at 5. Who would want to be a "mental nurse"?

The system is not only disastrous for recruitment and training; it is also monstrously inefficient. The nurse who looks after the patient, and therefore really knows most about him, feels cut off from his training and rehabilitation, in which she consequently tends to take diminished interests; she never has any contact with the relatives or the home except under the highly artificial conditions of visiting in hospitals. Yet, with a little additional training, a ward sister or a responsible nurse can be a very efficient social worker; indeed some of our nurses have managed to do very good social work without any special training in that department.

A DIFFERENT SYSTEM

If it is important that the interesting and rewarding jobs shall be returned to the nurse, it is equally important that people doing jobs like occupational therapy, workshop management and social work should have some experience with patients, preferably on the wards, as part of their training. To achieve these objects, we need a change in the present system of training, not only of nurses but also of the ancillary workers. Though vested interests will probably prevent effective action until we are faced with the imminent closure of wards and hospitals, I offer a suggestion for a realistic scheme.

The basic course in the care of mentally ill and mentally subnormal patients should last one year. The examination at the end of the year should be largely practical and the reports of the sisters in the wards where the nurse has been working would be of paramount importance. On passing the examination the nurse would get a rise in pay. If she were not ready to take the test after one year she could take it after two or three or any number of years.

Having passed the first-year test, the nurse could either continue to work in the wards or could continue her training in one of the special departments—e.g., general nurse training, occupational therapy, domestic science, social work, or physiotherapy. The better her qualifications, the more pay she would get and the more eligible she would be for senior posts. For example, one envisages a mental hospital of the future in which the matron has had, besides her one year's basic course, training in general nursing, domestic science, and perhaps occupational therapy. The head of the occupational therapy department would have the same status as the ward sister and, of course, similar basic training, but she would be expected to have taken occupational-therapy training, whereas the ward sister might be expected to be generally trained.

In introducing such a system we might have to face opposition from professional bodies; but the situation demands that the present system should undergo some such drastic reform.

Medical Education

RESEARCH ON TEACHING METHODS

Its Significance for the Curriculum

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THE chief criticism levelled at the basic sciences in the medical curriculum is that too much of the teaching programme is occupied with detail. Time could be saved (it is suggested) by teaching only broad principles, and could be devoted to more practical subjects and to the introduction of new ones. Anatomists in particular have much experience of this criticism. Naturally the critic implies that only broad principles are dealt with in his own subject.

This criticism has often been countered by the argument that nobody can comprehend the principles of any complex subject, or even acquire anything more than a superficial knowledge of it, without considerable knowledge of detail.

It is remarkable that, in spite of the long history of this controversy, the problem has not been investigated in the same way as other such research problems. In attempts to devise practical experiments on teaching courses, where groups of individuals, complex programmes, and testing systems are involved, serious complications are bound to arise; but, although these impose limitations on both courses and tests, they do not preclude meaningful answers to questions on the efficiency of such teaching courses.

PROBLEMS IN THE DESIGN OF THE EXPERIMENTS

The first problem is one of control, and of standards of comparison between groups. In comparing two or more teaching methods, one may use the performance of different student groups in one subject or the performance of one group in more than one subject. It is simpler to compare the performances of two groups of students, for if the subject remains the same but is treated in two different ways the objective tests must also remain the same. In a simple comparison between two teaching approaches the time devoted to each must not be varied.

The organisation of experimental courses presents other difficulties, not least of which may be the lack of a suitable textbook for the student's use, particularly if detail is to be excluded. Although the demarcation line between unnecessary detail and basic principles may be considered largely a matter of opinion, the only line which the student respects is the one inherent in the recommended textbook. Detail is therefore likely to be absorbed with the use of standard textbooks, to the study of which the student may give a disproportionately large part of his time.

In most experimental courses and tests the students are informed beforehand and asked to cooperate; this cooperation is always readily forthcoming. But in an experiment such as that reported here it is essential that the groups remain unaware that any investigation is being made. Further, since it is well known that in making such tests the investigator often obtains the results he expects, steps must also be taken to obviate this. If possible the tests should be arranged to assess the student's knowledge not only during the course but also after a period of time not specifically devoted to a study of the subject concerned.

OBJECTIVES OF THE RESEARCH

The controlled experiments reported here were designed to determine the immediate and later (recall) results of two different teaching approaches to a functionally important and complex area of the body. A course was devised in which the principles were stressed and details omitted, and this was compared to a course of the same length in which details were included. The performances of the student groups were examined by the same objective tests.

It might be expected that more knowledge would be shown by those to whom a detailed course in a restricted subject is given (and where the principles must of necessity be dealt with in the interests of clarity). This experiment, however, showed that the omission of detail, with emphasis on principles, resulted in improved total factual information, comprehension, and recall.

ORGANISATION OF COURSES

The groups chosen comprised the whole classes of two consecutive years and were of about the same tested ability, as shown in fig. 1. The shortest courses consistent

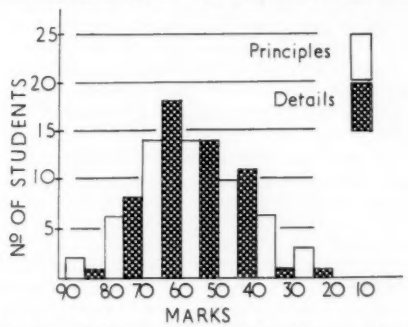


Fig. 1—Average of three control tests for the two student groups (P and D) show that they are of about the same ability.

with the acquisition of a reasonable knowledge of the region were organised; this was facilitated by previous experience and by comparison with normal and accepted programmes and tests. For the two groups the hand (including the forearm) was chosen as a suitable subject for the double appraisal.

Group P

The course for the "principles" group was devised to eliminate as much detailed anatomy as possible. All facts that the students were required to know were taught by the same instructor to the whole group during 3 lecture-demonstrations each week for three weeks. Printed dissection instructions specifically prepared for this course were used by the students and were accompanied by the customary demonstration facilities. The use of textbooks was excluded: students were told that the notes and diagrams on the lecture-demonstrations would replace the textbook and that all they would be expected to know would be covered by this means.

Group D

For the second group detail was emphasised. For example, the students' standard textbook was recommended for the osteology and syndesmology of the region, and practical work was carried out in detail according to the dissection manual. The 9 one-hour lecture-demonstrations were devoted largely to additional detail and supplemented the textbook and dis-

section-manual descriptions. To stimulate interest and attention, emphasis was laid on the functional importance of various details. Important variations in vascular patterns were stressed; in dealing with nerve and arterial supply the points of origin and entry into muscle of each named branch were defined; and tendon relationships at the wrist were treated in detail with emphasis on their functional importance.

PLAN OF TESTING SYSTEM

The subject of the research was introduced into the normal programme after the group had experience of the general subject and was accustomed to the testing system. Two identical tests were given in each group, and were necessarily devoid of questions pertaining to anatomical detail. The staff responsible for checking the answers to the tests had not been informed of the experiment and were different for each group.

The first test was given at the end of the first week while the second test was held for each group on completion of the course. In group P the second test was repeated four months later (recall test) and in group D it was repeated one month after completion of the course. The difference in the interval before the recall test was decided upon when the immediate control test revealed unexpected results; the objective was to weigh the advantage on the side of group D for this segment of the investigation.

Each test consisted of 30 questions and time was limited. No question had more than one answer, and all involved the recognition of some structure or part of a structure or was a concise question apposite to the structure indicated. Certain basic knowledge was always assumed—e.g., questions on naming of obvious structures were not asked as a preliminary to some other question. 3 marks were given for every correct answer, thus giving a maximum total of 90 marks.

Between completion of the course and repetition of the second test for group P, the students were on vacation; they were told that a revision test would be held at the end of this vacation. They were also told that the test would concern the entire previous year's work in anatomy; thus specific revision of the region was limited. During the interval of one month group D were also on vacation and were told that the revision test would concern only the previous term's work. Apart from this, care was taken in the experiment to make the only variable the total amount of information transmitted to the students.

ANALYSIS OF RESULTS

The number of students who obtained marks in each range of 10 between 0 and 90 is shown in fig. 2.

First Test

Fig. 2 (left) shows the results of the first test. Of the 54 students in group P, 36 obtained over 70 marks and 3 obtained the maximum of 90, whereas only 23 of 53 students in group D received over 70 marks and none obtained the maximum. The lowest mark in group P was 53, while 6 students of group D obtained less than 50.

Second Test

56 students of group P attended the second test as compared with 50 of group D.

Fig. 2 (right) shows a similar pattern to that of the first test. A larger proportion of students in group P obtained higher marks than those in group D; 9 students of group P came within the 80–90 range compared with only 2 students of group D. 9 students of each group received less than 50 marks.

Recall Test

Fig. 3 shows the results of the repetition of the second test. It should be noted that only 45 of group P attended, as compared with 52 of group D. Taking this difference into account, the results of each group closely correspond. 5 students of group D, compared with 2 of group P, obtained over 70 marks; and 5 in group D obtained less than 30, compared with 2 students of group P.

DISCUSSION OF RESULTS

These results demonstrate that the student group instructed with emphasis on principles (group P) obtained higher marks in the first two tests than those instructed in details (group D). The difference is greater than the difference between the average ability of the two groups as shown in fig. 1. Exclusion of detail from the questions should have resulted in the tests being comparatively more simple for those students in group D. A second factor which must be taken into account is that the course for group P was held shortly before the class examinations for the year. During this course therefore the students must have also been concerned with the revision of the previous year's work in both anatomy and physiology. In the recall test the difference in the results is further emphasised by the fact that group D were subjected to the recall test after one month on the basis of one term's revision instead of after four months' interval and one year's work for group P.

Reference to fig. 2 shows that the major differences between the two groups affected principally the more intelligent students. If the two results are combined it may be seen that 22 students of group P obtained marks between 80 and 90 as compared with only 9 of group D. In the range between 70 and 80 there were 35 of group P compared with 26 in group D. The conclusion must be that the more diligent student, while attempting to cover the course in full, directs too much effort towards attempts to master detail, or his apprecia-

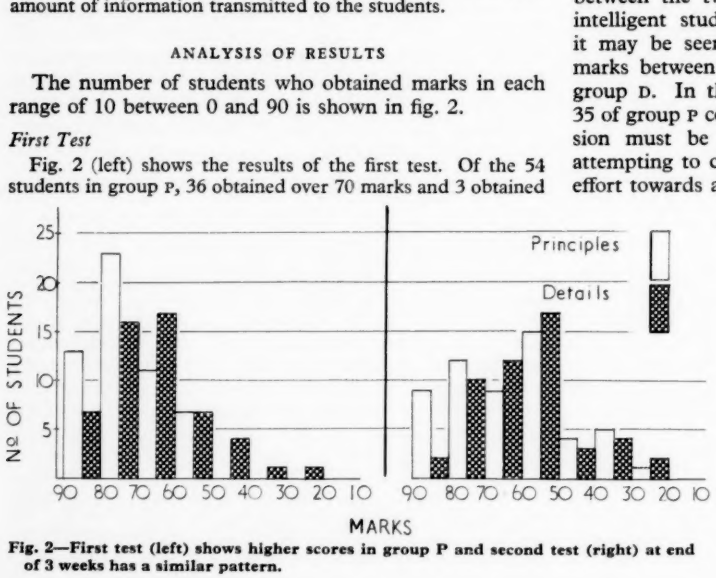


Fig. 2—First test (left) shows higher scores in group P and second test (right) at end of 3 weeks has a similar pattern.

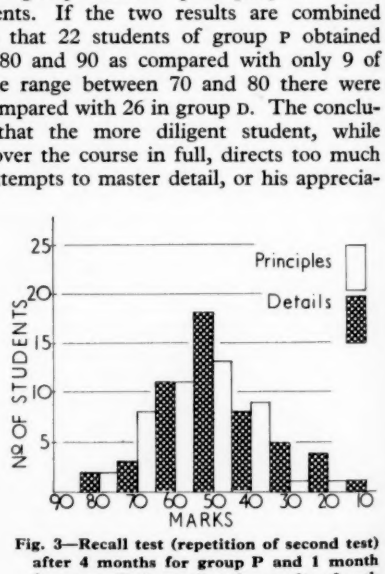


Fig. 3—Recall test (repetition of second test) after 4 months for group P and 1 month for group D shows that the results of each group cleosly correspond.

tion of the subject as a whole is confused by accumulation of detail. The less conscientious student, on the other hand, tends to neglect detail, and simply commits to memory information which he thinks sufficient to enable him to pass the test. Thus the difference between the two courses as described in this paper does not affect all students to the same extent, but chiefly the more industrious students.

IMPLICATIONS FOR THE MEDICAL CURRICULUM

This investigation shows that—provided instruction is efficient, properly planned, and properly organised—the traditional course in a complex subject can be significantly modified and assessed without difficulty and with the probability of improved results. It shows also that the quality of the basic teaching methods, at an advanced level, has a considerable effect on the student's efficiency, though before extensive reorganisation of the teaching programme in the medical curriculum could take place many questions still need an answer. Furthermore, it remains to be determined what minimum basic information is required on any particular subject.

What are the common elements in training for all the different practices and specialties in which the student may later engage? Undoubtedly one important factor is his ability to handle and apply the basic facts intelligently. Many questions on the value of the information at present transmitted in the curriculum produce vague answers. Experiments such as the one reported here could be devised to give more useful information on them.

When we have decided what to teach, intensive research must be done on the best way of teaching it. Efficiency in communication is a neglected field of university endeavour. Communication includes the use of some form of printed instructions or textbook, and for the present study special instructions had to be prepared. Nearly all student textbooks are based on the author's personal opinion rather than on the results of research into the effectiveness of such books as teaching aids. In the organisation of new and more efficient courses new textbooks must be designed which are appropriate to these courses.

Important factors are the student's personal effort to acquire not only facts but also practice in handling them. Teaching programmes must form, for the student, flexible guides to fact and theory and at the same time remain diverse enough to appeal to different aptitudes; this is also part of effective communication. Unfortunately, in many subjects innovation and diversity are at present almost precluded by the rigidity and traditional approach.

Occasionally it is suggested that the best means of carrying out the teaching programme is full-time instruction subject by subject. This has been adopted in some institutions and is stated to be an improvement; but it has not been objectively investigated. Many hold that part-time combined courses have advantages. Coordination (if not integration) with other subjects can be achieved, and good results in one teaching approach can immediately be applied to a whole area of study.

There is constant reiteration of the idea that teaching by people who are doing research provides the student with the necessary interest and stimulus to work. Thus current research in particular problems is equated with effective teaching. This idea, however, is not based on experimental evidence and is subject to many reservations. The nature of medical research is determined by the interests of each particular department and is often widely divorced from the teaching course.

Since the primary functions of the university are research and teaching, it seems obvious that institutions active in research can and should give attention to research into teaching methods. New programmes are common but no means are developed for ascertaining their practical value. This is very unsatisfactory. If methods for practical assessment of new teaching programmes, and for communication of facts and ideas, received even a small part of departmental research effort, improvement in the teaching approach to the whole medical curriculum would be accelerated.

SUMMARY

Controlled experiments showed that a teaching programme designed to emphasise principles and omit details gave better results than conventional instruction which included fuller information. Both immediate factual knowledge and recall were better in the group of students taught with less detail.

Scientific experiments can and should be designed to test the efficiency of various parts of medical courses, and particularly to assess the effectiveness of new teaching approaches and aids.

Conferences

HUMAN GENETICS

THE 2nd International Conference of Human Genetics was held on Sept. 7–12 in Rome, with Prof. L. GEDDA (Rome) presiding. We have selected below some topics of medical and social interest.

Prof. F. J. KALLMANN (New York), in his introductory address, remarked that 50 years elapsed between Garrod's concept of inborn errors of metabolism and the development of modern ideas of the chemical structure and function of the chromosomes. And it had taken more than 50 years from the recognition of the sex chromosomes to the discovery that children with Turner's syndrome had just one X chromosome, and Klinefelter's syndrome 2 Xs and a Y. The sharp accretion of new knowledge in human genetics brought new responsibility to apply it to the good of individuals and their progeny. It was all too easy to be pessimistic about the practical application of human genetics and to become more interested in the tools of genetic study than in their potential beneficiaries. A well-planned family was the essential unit of society, and one immediate application of human genetics was in genetic counselling. Advice by correspondence was not ideal, and there was need for a properly organised genetic counselling clinic at each main medical centre. Those concerned with counselling should have the ethical approach that the medical profession had evolved over the centuries. The counsellor must not arouse unnecessary anxiety, or fail to relieve tension where it existed. Every child born into the world had a right to a fair chance in life.

Negative Eugenics

E. SILVESTRONI (Rome) described the development of the first large-scale attempt at negative eugenics through counselling. He estimated that there were 2 million individuals in Italy heterozygous for the gene responsible for Cooley's anæmia, resulting in the death of 1000 homozygotes a year. By "pre-matrimonial prophylaxis"—that is, dissuading hetero-

zygotes from marrying each other—these deaths were preventable. Centres now established in many areas in Italy were engaged in testing every child in the elementary schools for heterozygosity.

Quantitative Traits

T. McKeown and C. R. Lowe (Birmingham) had found no evidence of bimodality in the blood-pressure readings of middle-aged men one of whose parents had died in early middle age. The whole distribution was shifted to the right of that of middle-aged men who had not had a parent dying young. They noted, however, that there might be a concealed bimodality.

R. B. Cattell (Urbana) described the partition of the variation observed in intelligence and other personality traits into genetic and environmental variation, and the interaction of gènes and environment, by a "multiple abstract variance analysis". Like other observers, he found about three-quarters of the variation in intelligence test score to be due to genetic variation. Similarly hereditary factors were more important for excitability, the cyclothymic-schizothymic scale, and super-ego strength. Tendermindedness versus toughmindedness, and general inhibition, were largely environmentally determined. Such assessments applied only to the particular culture being studied.

J. M. Tanner (London) described a study of the resemblance of anthropometric measurements of parent and child as the children grew from 1 to 7 years. For most measurements the parent-child correlation was small at birth but was approaching 0·4 by age 2 years. For many measurements the like-sex correlations (for example, mother-daughter) were higher than the unlike-sex correlations.

Blood-groups and Disease

J. A. Buckwalter (Iowa) noted that racial stratification as an explanation of the association of group A with gastric cancer and group O with duodenal ulcer had been ruled out by the finding of the association in Negroes, Indians, and coloured South Africans as well as Caucasians.

R. H. Osborne and F. V. de George (New York) reported that the association of group A and salivary-gland tumours was most evident in muco-epidermoid tumours of the parotid.

R. B. McConnell (Liverpool) reported a high concentration of Le^a and Le^b substances (in contrast to A, B, and H substances) in urine and suggested that the Lewis substance must play some part in the physiology, and perhaps the pathology, of the urinary tract.

F. Vogel (Berlin-Dahlem) reported the early stages of an interesting attempt to correlate the incidence of major killing diseases in the past with the frequencies of the ABO groups. Smallpox seemed to be more severe in A and AB individuals, and vaccination encephalitis seemed to occur more often in A and AB individuals. The smallpox virus contained an A antigen. Similarly the plague bacillus contained an H antigen, and there was a geographical correlation between high O frequency and freedom from a past history of plague epidemics. In contrast, in group-O patients the Wassermann reaction became negative more often after treatment.

Blood-groups and Paternity

H. Gurtler (Copenhagen) illustrated the value of blood-grouping in paternity cases for the determination of blood-group frequencies in the population. S. Lawler and R. Marshall had found in the family of a colleague no less than 5 instances of apparent exclusion of *maternity*, due to the presence in heterozygous form of the Rh chromosome -D-.

Biochemical Genetics

R. S. Krooth and others (Bethesda) reported the absence of catalase in cell cultures from skin biopsies of individuals with acatalasia, and a lowered level of catalase in cultures from heterozygous individuals. Cell lines from skin biopsies from homozygotes or heterozygotes for galactosæmia could also be distinguished by their reduced ability to metabolise galactose.

Chromosome Studies

C. S. Ford (Harwell) noted that 5 years ago Tjio and Levan had announced almost apologetically that man had 46 and not 48 chromosomes. Today we knew of 7 forms of anomalies of the sex chromosomes, 11 types of chromosome mosaicism, 3 types of autosomal trisomy, and several examples of chromosome translocation. It was remarkable that whereas with trisomy 21 (Down's syndrome) about half the offspring also had Down's syndrome, the 10 known children of women with trisomy of the X chromosome were all normal.

J. L. Hamerton and his colleagues (London) reported that translocation in the mother or father explained much but not all of the increased risk of a second mongol child to young mothers. It appeared that while mothers with a 15/21 translocation readily had children with Down's syndrome, fathers with this translocation only had phenotypically normal children, though many of these were also translocation carriers. This, however, did not seem to be the case with 22/21 translocations.

K. Patau and his colleagues (Wisconsin) suggested that many patients with multiple anomalies might be instances of partial trisomy and that each main anomaly was due to the presence in triplicate of a specific "trisomy locus".

Discussing natural selection and human chromosomal aberrations, L. S. Penrose (London) noted that while those heterozygous for a translocation had reduced fertility, those homozygous for such translocations might have normal fertility. There were no clear instances of chromosome inversion in man, but in drosophilia chromosome inversion might be associated with superfertility.

P. E. Polani (London) reported that nearly every patient with "ovarian dysgenesis" had a chromosome anomaly. In primary amenorrhœa the yield was about a third, and in mentally defective women the yield was 1%.

Sex-linked Inheritance

M. Lyon (Harwell) produced evidence from coat colour mosaics in mice that in the female, where only one X chromosome was active, this was sometimes the maternally derived and sometimes the paternally derived X chromosome. She suggested that this was the reason why women heterozygous for sex-linked mutant genes usually showed some effect of the gene, and this manifestation was usually variable.

Population Genetics

J. V. Neel (Michigan) emphasised the importance of polymorphic systems in which a number of alleles at a gene locus were present in the population, at a frequency which could not be attributed to mutation pressure, and therefore presumably had adaptive significance. At many gene loci there might be an optimal level of heterozygosity, and many malformations of ill-defined genetic basis might be due to the patient's failing to reach a level of heterozygosity obligatory for normal development. Heterozygosity could lead to the production of hybrid molecules, and not just to the mixture of two molecules. Thinking along these lines, several authors had reported studies on the effect of race-crossing, which might be expected to increase heterozygosity, and of inbreeding, which might be expected to reduce it.

W. J. Skull and J. V. Neel (Michigan) found that in Hiroshima, Japan, infant and childhood mortality were significantly associated with inbreeding, whereas in Nagasaki they were not.

E. Goldschmidt (Jerusalem) found in immigrants from Kurdistan that there was no increase in the number of stillbirths and malformations in children of consanguineous marriages, but that these children more often went to schools for the educationally subnormal.

C. S. Chung and N. E. Morton (Madison) found that outbreeding (race crossing) in Hawaii had no consistent effect on

malformations-rates in the hybrid children. There was a suggestion that the children of hybrid mothers had a lower perinatal mortality. These hybrid mothers had the low rate of monozygotic twin pregnancies typical of the parent of mongol race.

With regard to the social problem of differential fertility in civilised communities, J. V. HIGGINS and his colleagues (Minneapolis), in a large family study of the intelligence of both parents and their children, found that there were more children per family for parents with I.Q.s of above 130 and below 70 than for those in between. But the large family size of parents of low I.Q. was balanced by the finding that many of the sibs of these parents were childless.

C. O. CARTER (London) reported that the most recent figures for family size by socioeconomic class showed a relatively high fertility for those in the major professions and higher administrative posts in England, the U.S.A., France, and Sweden. He suggested that once all families were planned the negative correlation between family size and socioeconomic class would not only disappear but also become positive.

TUBERCULOSIS

FROM A CORRESPONDENT

FOR the 16th Conference of the International Union against Tuberculosis, in Toronto on Sept. 11–14, over 1500 chest specialists and others came from many countries. The proceedings not only reflected the main lines of current thought about the disease but they also emphasised the great gap between the economically favoured countries, in which eradication of the disease was a foreseeable attainment, and the less fortunate ones in which, as an Indian speaker said, a physician could not permit himself the luxury even of thinking about eradication while the disease remained uncontrolled.

Eradication

The final session of the conference was a stimulating discussion of eradication; and most of the preceding three days had led logically to it. It was generally agreed that proper chemotherapy would be the most important factor. The tools for effective treatment were available: we must learn to use them correctly. This was emphasised many times, particularly in the discussions on primary drug resistance, which was entirely preventable by adequate control of drugs within a country and proper use of them, and in the session on methods of improving and checking the taking of drugs by patients. The spread of resistant bacilli from person to person after inefficient chemotherapy may keep the disease alive for a long time in countries with all the economic and technical resources to eliminate it. And in the less fortunate countries primary drug resistance was an even bigger danger; for it was likely to be more prevalent where chemotherapy had of necessity been least efficiently used, through lack of drugs, personnel, and control. Moreover, the cost and other disadvantages of the "secondary" drugs prevented effective treatment of the resistant infections, with consequent greater opportunity for spread.

The prevalence of resistant cultures from apparently untreated patients could be an index of the efficiency of chemotherapy in the country during the preceding years. Accurate estimations of prevalence in different countries would be valuable. But at present, because of wide differences in bacteriological methods, comparison between the published figures was invalid—although much time was spent at one of the sessions in comparing them. The need for standardisation of methods, already advocated by the International Union, became more clearly apparent. Such standardisation would be a slow process; but a start had been made by the Union and there were indications during the meeting that some progress was being made.

The urgent need for better prescribing by doctors of existing drugs was mentioned several times. The valuable discussion of methods of getting patients to take the drugs prescribed demonstrated clearly how little we knew about the subject of long-continued self-medication, and how few people had, in the past, thought it important to find out more. The discussion may have stimulated others to inquire for themselves into an area of research which demands little more of the physician than a critical mind and a deep knowledge of the patients and their environment. A report from Tanganyika showed what can be achieved in this respect, both to increase knowledge and to improve the results of treatment.

Pulmonary Tuberculosis in the Over-50s

Some interesting differences emerged in ideas on the efficiency of treatment in these patients. While one investigator found no difference in the results of chemotherapy of the old and the young, both being equally good, others reported remarkably poor results in older patients. It seems likely that the differences lay in the efficiency with which the drugs were given, rather than in the efficiency of the drugs themselves in young and old bodies. Once again there emerged the well-known difference of therapeutic outlook, one school being content with nothing less than 100% success and the other accepting as inevitable a certain proportion of failures. The first school seems to be making ground; and some of the credit for this must certainly go to the International Union and meetings such as this one.

Chemotherapy

Ethionamide seems to be establishing itself as a valuable "second-line" drug, though its side-effects considerably limit its use. These were reported to be much less with the chlorhydrate of ethionamide given intravenously. Such treatment was not, however, applicable in large-scale treatment of patients in their homes. Tolerance seemed to vary in different groups of patients. Little was known of its effectiveness with isoniazid in previously untreated patients. An interesting report of a controlled trial in Morocco suggested from the preliminary results that the combination may be effective. Until more experience has been gained by other such studies, and by its wider use in those countries that most need an additional effective oral drug, ethionamide should not be dismissed as a drug of no value on a large scale.

* * *

Other sessions included discussions of the relationship of sarcoidosis and tuberculosis and the increasingly important subject of non-tuberculous sensitisation to tuberculin and infection with mycobacteria other than tubercle bacilli. In the discussion on the possible causative role of tubercle bacilli in sarcoidosis, the extent of the differences of opinion about many aspects of the disease was striking. Not even an agreed definition could be reached. That put forward by the American members of the panel did, as the British member pointed out, by excluding the possibility of tuberculosis being a cause of the phenomena, make further discussion logically impossible. However, the discussion, both logical and illogical, developed into a lively debate, with honours probably even at the end of it. Non-specific tuberculous sensitivity was being increasingly studied and there were new reports from the U.S.A., France, and Great Britain. The last, preliminary and so far unpublished, suggested that even in this country more practical account of it may have to be taken in the future.

The panel discussions and communications were remarkably free from the shibboleth and dogma that have at times marred this part of medicine. The general scientific standard was high. The contributions to research in tuberculosis by workers in Great Britain during the past fifteen years, particularly in controlled field investigations and detailed laboratory studies, have been outstanding; and this was apparent at this conference, even allowing for your correspondent's bias of quickened national pride during an international occasion.

In England Now

A Running Commentary by Peripatetic Correspondents

IN the ancient civilisation of the island kingdom of Quelconque, traces of which survive to this day, the religious customs are not without interest.

The average man, or woman, of this race—who was known in neighbouring countries as a Quelcon or simply as a 'con—did not believe strongly in a second life after death, being essentially pragmatic in outlook, but rather held the view that certain excellent people might be raised to a higher spiritual plane in this life. Clearly such individuals were valuable to the community; but how were they to be recognised, so that ordinary folk could draw the maximum benefit from them? The problem was eventually solved, at least for a time, by the institution of examinations, sometimes known as concours. It is believed that these were started by a small group of Higher Degrees (as the superior persons came to be called) who must have discovered each other and banded together out of mutual affinity and appreciation. Once in a while a concours would be announced and a great assembly of 'cons would be attracted by the possibility of being selected, or "passing", with all its attendant glory. They were in no way put off by the fact that several different kinds of ordeal were included in the procedure.

Gradually the numbers of aspirants grew unmanageable. Lest too many should become Higher Degrees, thereby weakening the prestige of the Order and reducing the labour force available for weeding the fields, sweeping the streets, and so on, it was made necessary to pay heavy fines of cattle and wives even to attend a concours. This sacrifice—especially the cattle—discouraged the indigenous and all too often indigent 'cons, but not the many visitors from foreign lands, who continued to attend, eager to discover the mysterious spiritual power which, it was said, belonged peculiarly to the Quelcon Higher Degrees. As time went by, fewer and fewer of the Higher Degrees were natives and the 'cons gradually ceased to believe in the myth at all.

This was not entirely a misfortune. Archæologists believe now that the escape of the popular mind from myth marked the transition from medievalism to the empirical tradition which has been the heritage of the Quelconque islanders ever since. It was about this time that an intellectual and political renaissance took root and spread from Quelconque, outwards across the archipelago of the Petits Confins, to what is now known as the Continent. No doubt many of those who might have exhausted their youth and intellect in striving to absorb the stereotyped dogma of the Higher Degree metaphysic at home instead went forth, unwanted and unlabelled, to use their talents abroad.

* * *

Scots who are disturbed by the heading "In England Now" may find comfort in my experience in Israel. I attended a conference at a psychiatric hospital attached to the Jerusalem University. The whole staff crowded each morning into the professor's room, and the doctor on duty gave a résumé of all admissions in the previous 24 hours. The conference was conducted in rapidly spoken Hebrew, but at the end the professor greeted me in English and introduced the speaker, saying, "He is from England." Dr. X protested with a broad accent which had not been apparent in his Hebrew—"From Britain, Sir, from Glasgow."

* * *

This has been a good seed-fruit year. All the edible berries—goose, straw, rasp, and now black—have flourished and been full of juice and good tastes (though, incidentally, in these parts there is not an apple or a plum to be seen on a tree). Never have I enjoyed so many so much. The rasps, in particular, went on for weeks and weeks, and the pleasure was augmented by the thought of all those little diverticula which, as I happen to know, adorn my descending colon, either disdaining the passing seeds and skins or, as I prefer to think, sucking them in, absorbing some last rich residue and expelling the utterly indigestible to go forth into the draught. Never has one of them complained of his diet.

It must be quite ten years since a barium enema brought them to light. Before it one of them may have been very gently complaining; scarcely since. "Well, I suppose I do nothing about them," said I. "Oh yes, you do," said He, "you do really avoid all those seeds and small residues. Strawberries have a specially bad reputation with us surgeons." "Oh," said I, a bit uncommittally, and avoid them I did for quite a week, perhaps ten days. By then it was clear that if I kept it up I should not only miss many of the all too rare sweets of later life but be an intolerable nuisance to family and friends. "No, he mustn't take proper marmalade, only honey or jelly, I'm afraid. I'm so sorry, but strawberries are *verboten*." "Throw medical advice to the dogs, I'll none of it," I said. Tomorrow, even tonight, the final, fatal, painful blow may fall and it may be said of me, as of Jim the nurse-hand-slipper, "He would *not* do as he was told"; but there, next week the thousand megaton hydrogen what-not may fall too. "Gather ye seed-fruits while ye may."

* * *

My peripatetic colleague's comments about Baxter prompt me to inquire whether that other character of the advertisement pages, Mrs. K., the indomitable she, all quips and curls, might be *his* favourite patient. Is he the doctor who approves of the favourite drink, with its 126 calories in one glass? I wonder, too, how long it will be before the chief comes round and asks why he has not thrown the offending bottle out of the window, for if she is not on an 800-calorie diet, or less, she jolly well ought to be.

* * *

"Please to tell me—my English is not good, you have much rheumatism in England—No?"

"Oh, not really. We have a certain amount in our older age-groups, particularly in those over 90. The trouble is that we have so many people over 90—probably more than in any other country in the world."

"Ah, but in Hulgaria we have many people of 100."

"Oh yes, I'm sure; but we have a greater percentage of old people and therefore perhaps a greater percentage of rheumatism."

"But why should this thing be—you have more of these old people?"

"Oh I suppose we eat well, sleep well, and don't worry."

"We eat well and these other things you say in Hulgaria."

"Then I suppose it must be the Gulf Stream."

"Ah yes, that is it. It is the Gulf Stream that we have not."

* * *

A typical hysteric, immature
Emotionally, a slave to limelight's lure—
Remember for the analytic cure—
Œdipus!

Replete with doubts, obsessed, his mind is racked
Whene'er he fails in his compulsive act;
The origin of this peculiar fact—
Œdipus!

Anxious and apprehensive every hour,
Her sleep disturbed by fearful dreams that lour,
The molehills all transformed to peaks that tower—
Œdipus!

Fatigued in mind and body, and the head
O'erburdened with a heavy weight like lead,
The neurasthenic's energies have fled—
Œdipus!

Whichever type neurotic comes today,
Whatever style the dynamisms play,
With confidence the analyst can say—
Œdipus!

Letters to the Editor

THE N.H.S. IS BIG BUSINESS

SIR,—Dr. Seale's article of Aug. 26 is like the first glow of dawn on a murky sea. Let us give thanks that such sound sense comes from somebody of authority and wisdom within the Health Service. Let us give even greater thanks that the memorandum on which his article is based was submitted by request to the Minister's Advisory Council, whence it must surely reach the Minister himself, who is wise enough and big enough to take notice.

But I must at once declare interest. I am a management consultant, responsible for over fifty hospital work-study surveys in three different regions. But just as my organisation was getting absorbed in hospital problems and I was convinced that my survey teams could make some impact we were virtually banished by a circular, issued by the Minister's predecessor, forbidding hospital authorities to engage and pay outside consultants from Exchequer funds.

This same circular encouraged regional hospital boards to appoint one work-study officer each, whole time. Remembering that a team of four work-study consultants took some five months to cover the domestic assistants, orderlies, and porters in two hospitals, I wondered how long it would take one man to survey all departments of a hundred or more hospitals.

The numbers of work-study officers have since been allowed to grow, so that the time needed to cover the hospital service can now be reckoned in decades instead of generations. But management is scarcely touched at all.

Dr. Seale gives a fillip to my conceit by confirming some of the gospel I have been preaching for years, such as that the N.H.S. is big business and must be run as such, that it lacks the equivalent of managing directors, and that there is a lamentable resistance to delegation, particularly financial delegation. But his recommendations go further than my terms of reference have ever taken mine and show how the central planning, administration, and finance should be overhauled.

Until this is done the hospitals and groups will have no authority to look to their own internal efficiency, which some group secretaries have long been anxious to do.

Economy, Dr. Seale rightly says, is not an end in itself. Money saved should be used to increase efficiency. One of the reasons why the results of work study have tended to be measured in terms of financial savings is that efficiency cannot be measured by any recognised yardstick. But a way found to do things more economically is nearly always a way to do them more efficiently.

A rough calculation, based on the financial results of my teams' surveys, shows that the hospital service could save £10 million a year on ancillary staff alone and be made the more efficient for it. A useful sum to apply to the purchase of quality.

London, S.W.1. S. J. NOEL-BROWN.

NURSING CURRICULUM

SIR,—For over twenty years I have lectured to nurses in medicine and marked State examination papers. I continued to do them because it gave me ideas how students in other hospitals answered questions and I am often surprised at the amount of knowledge they have. Now we are to have changes which neither the medical profession nor the sister tutors have had an opportunity to discuss. In future medical, surgical, gynæcological, and other subjects are going to be mixed up in two general papers. For this reason I replied to the General Nursing Council saying that if this was so I must resign because I am incapable of marking gynæcological or orthopædic questions and probably also surgical questions.

I can see endless disputes between the medically qualified examiners and the nursing examiners if this is allowed to happen. Even at this late hour can we not have "one general medical and one general surgical paper" instead of two general papers set by an examining board of two nursing tutors, one physician, and one surgeon? I feel sure this would help recruitment of examiners, although even so I can see trouble in the joint marking by a physician or surgeon and a nurse.

Miss Louden (Sept. 2) raises other points. She says lectures are given at an "arbitrary" period in a nurse's training. "Arbitrary" according to the *Concise Oxford Dictionary* means "Derived from mere opinion, capricious, unrestrained, despotic: (Law) discretionary". Presumably she is using the word in the legal sense; if not I can assure her that sister tutors choose the time for lectures very carefully. I for one would find it difficult to give as she suggests an elementary course early in a nurse's training followed by a specialised course later. It would certainly mean more lectures.

For some time I have advocated without success that staff nurses should be given postgraduate lectures and indeed that they should have the opportunity of getting a certificate equivalent to that issued by the midwife's board; and this should be in a specialty of their choosing.

I therefore summarise by making two constructive criticisms:

(1) For the sake of the nurse and the teacher, we should maintain a division between medicine and surgery.

(2) Give the State-registered nurse a better opportunity for postgraduate education in a specialty of her own choosing.

Rugby. R. E. SMITH.

HEATSTROKE DURING AND AFTER ANÆSTHESIA

SIR,—Your report of the death of a young policeman in Manchester from heatstroke in the operating-theatre (July 15, p. 164) is a further reminder that the microclimate of the unconscious patient, unacclimatised to operating-theatre conditions, and lying in still, saturated air under the towels or waterproof sheets, may be more severe than that imposed by the ambient air on the conscious occupants of an overheated theatre. He is not in a position to do anything if the mechanisms which regulate his body temperature are inadequate to cope with the heat load.

Harris and Hutton [1] also reported, from Guy's Hospital, three similar deaths—of a child, a young man, and another patient whose age was not given—in July and on days which were warm but not excessively hot. One recalls a query from a surgeon in Singapore as to whether atropinisation of two patients before thyroidectomy might have contributed to their demise at operation. Unexpected deaths in such circumstances, particularly when there is a sudden change in climate, are perhaps more common than the hospital authorities suspect.

Paradoxically, it may be more important for those who live in temperate regions to be aware of the dangers of climatic excess than for those who have lived with a hot climate all their lives, who are fully acclimatised to its vagaries.

The patient's condition is only part of the story. A few years ago, provoked by a lively correspondence in the *British*

1. Harris, T. A. B., Hutton, A. M. *Lancet*, 1956, ii, 1024.

Medical Journal on the optimum design of a surgeon's cap to prevent sweat dripping off his brow on to the patient, I had the temerity to inquire, after discussing the operating-theatre environment with surgical colleagues, whether sufficient thought had been given to the effect of sweat-provoking atmospheres on the efficiency of operating teams.[2] I asked whether "the elucidation of some of the climatic problems of surgery might be assisted by more detailed studies than have been made in the past of the thermal environment of surgeons, anæsthetists and nurses and of their patients, in the operating theatre and in the wards, and not only in parts of the world where extreme climatic conditions are encountered, but also in the so-called temperate zones". Reliable data obtained in the course of such investigations seemed to me to be of fundamental importance to the design of operating-theatres and to the operation of their ventilation systems so that the maximum benefit would accrue from their use, as well as to the welfare of the patient.

The American Society of Heating, Ventilating and Air-Conditioning Engineers,[3] in the society's "Guide", still tells us what it has told us for many years, however, that "little is known about optimum air conditions for maintaining body temperature during anæsthesia and the immediate post-operative period"; although some broad guidance is given to the engineer and there has been at least one valuable contribution in the interim by Clark, Orkin, and Rovenstine.[4] These investigators concluded from studies on 212 patients in New York that the wet-bulb temperature of the ambient air provided the most satisfactory measure of the "thermal tolerability" of the operating-theatre environment, and that when the wet-bulb temperature exceeded 75°F the body temperature rose progressively. The average individual in the United Kingdom during the summer months is usually acclimatised to lower levels of environmental warmth than the average person in New York. In the only fatality reported by Harris and Hutton where the operating-theatre temperature is given (case 2), the wet-bulb temperature was 75°F. On the other hand, surgeons have operated on patients acclimatised to the tropics in non-air-conditioned operating-theatres for many years in areas where the daytime wet-bulb temperature rarely falls much below 75°F.

Heatstroke and heat exhaustion are preventable in most circumstances, and, particularly in young adults, both conditions are eminently treatable if recognised in time. In the case you report, Sir, the jury express the view that "serious thought should be given to installing temporary ventilation equipment in existing operating theatres", and they might well have expressed themselves more forcibly. Serious thought should also be given to the need for defining with greater precision than hitherto the levels of environmental warmth which are potentially dangerous to the unconscious patient, and to the early recognition of the hazard to which he is exposed when these levels are exceeded. Even if the day comes when precise environmental control is generally available in most hospitals in Great Britain, this information will still be needed in field hospitals in time of war, in emergency elsewhere, and in those countries which are unable to afford this undoubtedly costly therapeutic aid. Perhaps it is already available! If so, it should be promulgated to those who need it. If not, steps should be taken to obtain it. Surgical techniques are so successful today that it is unthinkable that they should occasionally be defeated because of avoidable neglect to provide the surgeon and the patient with an environment which is conducive to efficiency on the one hand and survival on the other.

Office of the British Navy Staff,
Washington, D.C., U.S.A.

F. P. ELLIS
Surgeon Captain, Royal Navy.

2. Ellis, F. P. *Ann. R. Coll. Surg. Engl.* 1953, **12**, 369.
3. Heating, Ventilating and Air-Conditioning Guide. 1960.
4. Clark, R. E., Orkin, L. R., Rovenstine, E. A. *J. Amer. med. Ass.* 1954, **154**, 311.

A ROAD SIGN REMOVED

SIR,—The Canvey Island Road Safety Committee has taken notice of the statement in your leading article of Aug. 26, concerning "eloquent pleas for caution", and as you reported last week, have decided to remove the main road-safety notice board in the district for an experimental period of one year. I would say that although the accident statistics for the experimental period will be compared with the accident statistics for the preceding twelve months, it is acknowledged that the period of the experiment will probably be too limited to prove or disprove your hypothesis.

It is hoped, however, that other responsible organisations will follow the example of my Committee, for is it not true that the local application of a "plastering" of posters is inadequate to deal with road accidents which now challenge for the position of the greatest public-health menace of our age. What is needed is a good dose of the old universal panacea "More Money"—this time for better roads.

Council Offices,
Canvey Island,
Essex.

G. EDWARDS
Road Safety Secretary.

ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

SIR,—The conclusion by Dr. Hilden and his colleagues (Aug. 12) that anticoagulant therapy is not indicated in acute myocardial infarction is of great importance if the premises on which it rests are valid. However, this is open to very serious doubt.

The authors are of course quite aware that the two groups of the case-material must be comparable; if not, no conclusions can safely be drawn. Scrutiny of their paper reveals an important fact. After exclusion of cases diagnosed only post mortem or more than seventy-two hours after the onset of infarction 1016 patients remain. Of these, 216 died within forty-eight hours, and 800 patients are left. Only these constitute the part of the material statistically evaluated, *except* in the estimation of the incidence of bleeding (p. 330, first column). Here all 1016 patients are considered, and it is seen that 426 belong to the treated group and 590 (the cipher given—530—is a misprint) belong to the non-treated group. As the statistically evaluated groups comprise 371 treated and 429 control cases it follows that within forty-eight hours 55 patients of the treated group and 161 of the non-treated group died (see accompanying table).

MORTALITY IN TREATED AND NON-TREATED CASES

–	Treated	Non-treated
No. of patients	426	590
Died within 48 hours ..	55 (12·9%)	161 (27·5%)
Total deaths	140 (32·9%)	270 (44·1%)

Thus the "early" mortality-rate in the non-treated group is more than double the rate in the treated group. This difference, which is statistically highly significant, definitely demands an explanation as it may imply that the two groups are not comparable and the authors' conclusion is thus unwarranted.

The authors' finding of an insignificant difference between the mortality-rates of the treated group and the control group might be due to this great difference in the early mortality-rate.

Without the exclusion of the 216 patients who died within forty-eight hours the results are as seen in the table. The difference between the mortality-rate in the treated group (32·9%) and in the non-treated group (44·1%) is statistically highly significant ($P < 0.001$).

Unless the exclusion of 216 early deaths is justified and a sufficient explanation of the causes of the very great difference in the distribution of these between the two groups can be

given, it appears to be impossible to accept Hilden et al.'s conclusions.

It may also be of importance to the validity of the conclusions that the incidence of bleeding in Hilden et al.'s material is high—19% in the treated group of 426 cases. In two series published by me [1] the incidences were 4% in 174 cases and 3% in 166 cases. Wright et al.[2] had in 589 patients 7·9% cases with bleeding caused by treatment. Hilden et al. had 4 deaths caused by bleeding and furthermore "in several cases it [bleeding] was fairly severe" (p. 330, first column). Despite the vagueness of this statement it is quite clear that severe hæmorrhage occurred too frequently in Hilden et al.'s treated cases.

In Wright et al.'s treated group the incidence of severe bleeding was 0·8%. In the literature incidence of severe bleeding varies between 0 and 2·5%. The last-mentioned value—2·5%—is from the publication of Bresnick et al.[3] The incidence of severe bleeding in Hilden et al.'s material seems to be of the same order of magnitude. Bresnick et al. themselves clearly considered their incidence too high, and they definitely stated that in the large general hospital the control and the system they used at that time was *not* satisfactory. They emphasised, however, that their results in no way indicated that dicoumarol might not be of value in acute myocardial infarction, but constant careful supervision was a prime requisite for successful results.

This is still the crucial point in therapy with anticoagulants.

First Medical University Department,
Aarhus, Denmark. C. HOLTEN.

"NO SPECIALISED EXPERIENCE"

SIR,—As the initiator of the advertisement [4] to which Dr. Jarrett refers (Sept. 2), I feel called on to reply to his comments.

It is important in selecting someone for such an important post as senior registrar, with its implication of later consultant rank, to think of what the candidate will be like in three years and not what he is like when first appointed. If he has a sound knowledge of general medicine when appointed he can acquire a reasonable understanding of dermatology in three years which will go on developing. If, however, he has never had an adequate training in general medicine but has turned too early to dermatology, he will always have the narrow outlook for which dermatologists have been criticised in the past. My colleagues and I can teach a man dermatology but we cannot teach him up-to-date general medicine at this stage. I agree that failure to attract good young men to dermatology may depend to some extent on lack of inspiration from teachers, but it is only when dermatology is integrated with general medicine, as is happening more and more today, that it becomes really exciting. When it is based solely on "the anatomy, physiology, and pathology of the skin" it is much less inspiring.

Dr. Jarrett also suggests that an appointment of this type lessens the chances of promotion for those already in training and causes frustration. I do not think he need be afraid on this score. Many of my colleagues in other teaching centres have told me of their acute shortage of suitable candidates. We have not so far had a single application either from a dermatological registrar or one in general medicine, and yet there is a splendid opportunity for steady promotion to consultant rank with a very good chance of a post at a teaching hospital.

I hope this letter will catch the eye of some young registrar and tempt him to take up the exciting and rewarding study of dermatology.

Dermatology Department,
Leeds General Infirmary. F. F. HELLIER.

1. Holten, C. *Acta med. scand.* 1951, **140**, 340; *ibid.* 1956, **155**, 15.
2. Wright, I. S., Marple, C. D., Beck, D. F. Myocardial Infarction. New York, 1954.
3. Bresnick, E., Selverstone, L. A., Rapoport, B., Cheskey, K., Hultgren, H. N., Sise, H. S. *New Engl. J. Med.* 1950, **243**, 806.
4. *Lancet*, Aug. 19, 1961, advertisement, p. 36.

VACCINATION AGAINST POLIOMYELITIS

SIR,—Your leading article of Sept. 9 fails to make clear the difference between the Sabin and the Cox strains of attenuated polioviruses. The strains developed by Sabin have shown themselves to be completely safe, not only for vaccinated individuals but also for their contacts, whether adults or children. In fact, spread of Sabin's strains to adults did not occur in the studies reported by Gelfand et al. in 1959.[1] In the Cincinnati study which you quote,[2] despite the fact that among young parents of pre-school children in the higher-income families 46% of the fathers and 25% of the mothers had not received a single dose of Salk vaccine, there were no untoward occurrences.

The strains developed by Sabin are the only ones approved by the licensing authorities, either here or in the United States, and no valid comparison can be made between them and the Cox strains which exhibit a much higher level of monkey neurovirulence.

Your final paragraph does not take account of the current global shortage of killed vaccine of adequate potency, free from S.V.40, and makes light of the difficulties which still delay a satisfactory quadruple vaccine. The fact that these have stemmed mainly from the failure of one or more components to exhibit satisfactory stability in combination does not appear to bode well for the "incorporation of newly emerging pathogenic viruses". Furthermore, an increase in the components of a polyvalent vaccine is very likely to lead to a decrease in effectiveness of the individual antigens concerned.

P. B. STONES
Sandwich. Adviser, Biological Studies, Pfizer Ltd.

HÆMAGGLUTINATION BY ADENOVIRUSES

SIR,—The hæmagglutination activity (H.A.) of adenoviruses has recently been demonstrated using human erythrocytes. The red cells of certain laboratory animals were also found to be sensitive to the hæmagglutinating activity of adenoviruses.[3–5] So far, however, no animal has been found to have red cells equally sensitive to all strains of adenoviruses. The work recorded here was undertaken to examine the red cells of a greater number of different mammals and birds, to determine their sensitivity to the H.A. activity of adenoviruses. The specificity of the reaction, if present, was also examined.

The H.A. of 42 strains belonging to the first 16 serological types of adenoviruses were studied using red cells from 97 animals (mammals and birds) kept in the zoo, from some laboratory animals (rat, guineapig, mouse, rabbit), and from 56 human beings of different blood-groups. The experiments were performed with virus suspensions of 10^{-4} to 10^{-5} T.C.I.D.$_{50}$ per ml. Out of the 47 birds tested, H.A. was observed with the red cells of 26 with one or more strains in 1 : 16 to 1 : 128 titre. Low-titre H.A. was observed with one or two strains with the red cells of 7 out of the 33 mammals tested. Results with 17 additional animals from the zoo did not yield acceptable results. Of the laboratory animals tested, no H.A. was found with the red cells of the 10 rabbits examined, while a few virus strains gave 1 : 16 to 1 : 32 titres with red cells from guineapigs and mice. With the red cells of the 38 rats tested high H.A. titres (1 : 128 to 1 : 512) were obtained with serotypes 9, 10, 13, and 15. With these red cells the extreme H.A. titre obtained was 1 : 16,384. Of the 56 different red cells of human origin some gave positive H.A. of 1 : 16 to 1 : 64 titres with serotypes 9, 10, 13, and 15. No correlation between

1. Gelfand, H. M., Potash, L., LeBlanc, D. R., Fox, J. P. *J. Amer. med. Ass.* 1959, **170**, 2039.
2. Sabin, A. B., Michaels, R. H., Spigland, I., Pelon, W., Rhim, J. S., Wehr, R. E. *Amer. J. Dis. Child.* 1961, **101**, 546.
3. Rosen, L. *Virology*, 1958, **5**, 574.
4. Rosen, L. *Amer. J. Hyg.* 1960, **71**, 120.
5. Buckland, F. E. *Nature, Lond.* 1959, **183**, 1276.

the blood-group and H.A. was found. No species were found to have red cells yielding uniformly positive H.A. with all the strains examined. The H.A.s found could have been inhibited by strain-specific antiviral rabbit sera, proving the specificity of the reaction.

Of the 42 virus strains tested 14 gave no H.A. whatever, while the other strains gave low-titre H.A. with red cells of only one or a few species. Only 6 strains were found to hæmagglutinate the red cells of more than 5 species. These were: the 9/2 strain of 24, the 10/1 of 7, the 10/3, 11/3, 13/2 of 6, and the 15/1 of 7 species, the numerator representing the serotype, and the denominator the different strains belonging to the same serotype.

Our results have shown that the H.A. of adenoviruses was a specific, though highly complex, phenomenon. The red cells agglutinated in high titres by certain types of the virus were either not agglutinated by others, or only moderately. Strains belonging to the same serological type reacted quite differently with the same red cells under identical experimental conditions. Further, the red cells of certain individuals belonging to the same species (human, rats) were differently agglutinated by the same virus strain. The latter phenomenon has been observed by others.[5] The detailed study of the red-cell receptors [6] and inhibitors will probably help to elucidate this problem.

Our experiments will be published in detail elsewhere.

I. NÁSZ
ANNA LENGYEL
P. DÁN
GIZELLA KULCSÁR.

Institute for Microbiology, University Medical School, Budapest.

LANGUAGE: THE LOST TOOL OF LEARNING

SIR,—I have followed with vivid interest and with fluctuating hopes the correspondence "provoked" by Sir George Pickering's lecture upon *the* lost tool of learning, and since carried on in your pages with a variety of linguistic tools.

Is it unseemly to suggest that the moment may have arrived to recall that language is not the sole tool of learning, but that this tool, its formation and its use, largely derive from ideas, and that without some reference to these no discussion on language can have much point?

The 17th-century French literary critic, Boileau, seems to have been aware of this when he advised his contemporaries thus:

> Avant donc que d'écrire apprenez à penser . . .
> Ce que l'on conçoit bien s'énonce clairement,
> Et les mots pour le dire arrivent aisément.

The aphorism might well be inscribed upon the walls of every research department.

London, W.1. F. M. R. WALSHE.

HELLENOMANIA—HELLENOPHOBIA

SIR,—Dr. Jackson's recent article on pseudo-Greek words was stimulating. Years ago scientific workers of different disciplines could talk and write so that each could understand the other; nowadays it is difficult for practitioners in one branch of medicine to understand fully the communications from other specialties. Research is adding so many new concepts and terms that an effort must be made to reduce not only the number of "made-up" names when an older term qualified by an adjective would do but also to reduce the redundancy of old names, for instance many of the eponymous terms.

We must also resist the efforts of the pedants who bring out a new name whenever a new theory of causation is proposed (why must theories be "advanced"?). At the same time, let us do away with some of the other clichés (for example, "steroids were exhibited", when we mean nothing of the sort); and let us also be grammatical ("No abnormal physical signs were found" would make a child fail the 11+ examination).

Many of our clinical notes and instructions have to be read by nurses, laboratory technicians, physiotherapists, radiographers, and electrocardiographers, so that the investigation or treatment can be modified to the circumstances. Surely we have a duty to speak in terms they can understand?

Finally, Sir, may I make a plea for some Basic English in Medicine?

St. James's Hospital, Leeds. N. A. NICHOLLS.

EFFECT OF A NEW ANTIVIRAL SUBSTANCE (XENALAMINE) IN CHICKENPOX

SIR,—We previously found the biphenylglyoxal, xenalamine (*p* -[α-ethoxy-*p*-phenylphenacylamido] benzoic acid), effective in man against influenza and herpes simplex.[1,2] We have now studied its effect in the prophylaxis and treatment of chickenpox.

We carried out double-blind trials on children between three and five years old in a public nursery at Concordia Sagittaria, near Venice.

The results of a short-term trial have already been reported.[3] This further long-term prophylactic trial was performed on 40 children who had not already had chickenpox, at a time when several of the others had contracted the disease.

The tablets of xenalamine and placebo were identical in appearance and taste. 20 children, randomly distributed, received placebo and 20 xenalamine; the identity of the tablets was not known to the doctors or nurses. Treatment lasted twenty-five days and 5 tablets (1250 mg.) were given daily.

TIME TAKEN FOR VESICLES TO FORM CRUSTS (no. of patients)

Days	Placebo	Xenalamine
1	0	4
2	1	1
3	2	1
4	3	0
5	2	0
6	1	0

10 children given the placebo fell ill, and 3 who were given xenalamine. In addition 1 child who received xenalamine for only two days became ill eight days later.

In the children who were given the placebo the disease followed its characteristic course: there was fever and a pruritic rash. The typical vesicles appeared successively on the trunk, face, shoulders, and occasionally the extremities. Those receiving xenalamine were afebrile, and only erythematous papules developed—in fact, they had the disease in its mildest form.

Thus xenalamine greatly reduced the incidence of chickenpox (from 50% to 15% in our two groups); furthermore the illness assumed a much milder form in those given xenalamine.

The trial was extended; and the 13 children who contracted chickenpox during the prophylactic trial continued to receive the same tablets as before in an identical dose (5 tablets, 1250 mg.); 3 others who became ill before the prophylactic trial started were given xenalamine.

In the children given the placebo fever developed, as well as successive crops of vesicles in the first two or three days. In those given xenalamine they were absent. The time taken for crusts to form differed strikingly in the two groups; the state of the 3 children who had been given

6. Kasel, A. J., Rowe, W. P., Nemes, J. L. *Virology*, 1960, **10**, 388.

1. Leonardi, G. *G. veneto. Sci. med.* 1960, **15**, 233; *G. Clin. med.* 1961, **42**, 146.
2. Leonardi, G., Moro, V., Zulian, G. *G. Mal. infett.* 1960, **12**, 419.
3. Leonardi, G., Ghio, T., Toppan, S. *Minerva Med.* 1961 (in the press).

xenalamine throughout improved after only one day's treatment.

We conclude that xenalamine is effective in preventing chickenpox, moderating the course of the disease, and speeding recovery. This is a further example of its antiviral activity in virus diseases affecting the skin or mucous membranes.[4–9]

Xenalamine is manufactured by Vister Laboratories, Casatenovo Brianza, Como, Italy.

Department of Medicine, St. Thomas' Hospital, Portogruaro, Italy. GIUSEPPE LEONARDI
GINO ZULIAN.

Public Health Department, Venice. TOMMASO GHIO.

EFFECT OF AURIC IONS ON TASTE

SIR,—An aqueous solution of sodium sulphite (Na_2SO_3) tastes characteristically bitter-salt. The taste of sulphur dioxide (SO_2) gas is well known. By an accidental observation we found that after a dilute solution of hexabromoauric acid (H_3AuBr_6) had been in the mouth for a short time and the mouth had been subsequently rinsed with water, both Na_2SO_3 and SO_2 taste sweet, like sugar or candy. The smell of SO_2 somewhat obscures the effect, and care should be taken that it only enters the mouth.

The ferric (Fe^{+++}), ferrous (Fe^{++}), cupric (Cu^{++}), and cuprous (Cu^{+}) ions have hardly any effect on the taste of the two compounds mentioned; certainly no effect towards sweet taste. The argentous (Ag^{+}) ion makes them taste more bitter and distasteful, but certainly not sweet. The Ag ion makes a cigarette distasteful; but the effect of the Au ion on the taste of cigarettes is very much less pronounced.

The effect described is very impressive, and the experiment can be easily performed. It is a good example of the so-called taste contrasts.

The Negev Institute for Arid Zone Research, Beer-Sheva, Israel. FRANCIS DE KŐRÖSY.

TUBERCULOUS ADDISON'S DISEASE

SIR,—The interesting report by Dr. Annear and Dr. Baker (Sept. 9) on a case of Addison's disease "cured" by anti-tuberculosis treatment provokes some comments on the nature of chronic adrenocortical failure.

That the antituberculous drugs were an effective treatment for a presumed tuberculous infection of the adrenal gland is apparent from the clinical course of the disease; but the fact that supportive corticosteroid drugs were not necessary to maintain apparent normal wellbeing after the withdrawal of antituberculous drugs is not sufficient evidence of cure. That is, reduced adrenocortical reserve may persist.

On the last occasion when a corticotrophin stimulation test was carried out there was no increase in the urinary 17-ketosteroid excretion. This is surely good evidence that adrenal reserve is limited.

I have recently seen adrenocortical insufficiency manifested in a young man by the sole symptom of pigmentation. Blood-pressure and serum electrolytes were quite normal, but corticotrophin stimulation did not result in an increase in urinary 17-ketosteroids or ketogenic steroids above control values. Najib abu Haydar et al.[10] have drawn attention to this condition of reduced adrenal reserve and indicate the usefulness of the corticotrophin stimulation test.

4. Cavallini, G., Massarani, E. *J. Med. Pharm.* 1959, **1**, 365.
5. Cavallini, G., Massarani, E., Nardi, E. *ibid.* 1960, **2**, 99.
6. Magrassi, F., Cavallini, G., Massarani, E. *Arch. ges. Virusforsch.* 1960, **10**, 19.
7. Magrassi, F., Altucci, P., Buonanno, G. A., Buoninconti, R., Di Simone, A., Lorenzutti, G., Pecori, V., Sapio, U. *G. Mal. infett.* 1960, **12**, 131.
8. Magrassi, F., Altucci, P., Buonanno, G. A., Lorenzutti, G., Sapio, U. *Minerva Med.* 1960, **51**, 233.
9. Leonardi, G. *Recenti Progr. Med.* 1961, **30**, 275.
10. Najib abu Haydar, J. R. St M., Reddy, W. J., Laidlaw, J. C., Thorn, G. W. *J. clin. Endocrinol.* 1958, **18**, 121.

It seems likely that the case described by Dr. Annear and Dr. Baker comes into this category although the patient has remained well for several years without treatment. The test of cure must be a satisfactory response to adrenal stimulation. This criticism in no way detracts from the admirable treatment which may have resulted in compensated adrenal insufficiency rather than cure.

Institute of Clinical Research, Middlesex Hospital Medical School, London, W.1. HILLAS SMITH.

SIX CHILDREN WITH COUGHS

SIR,—Dr. Yudkin (Sept. 9) asks himself two pertinent and penetrating questions: "What is the matter with the patient", and "Why has he come?" Although he implies the most important and fundamental question of all, he does not actually state it. The question is, of course, "Who is the patient?" In his cases the problem arose as to whether the child or the mother was the patient.

Having discovered in these quoted cases that there are at least two diagnoses, or, as I prefer to think of them, alternative diagnoses at different levels, he may have discovered that he could not do anything about the "condition" diagnosed at the most significant level. He is a pædiatrician; he can go no further. The general practitioner on the other hand is the only one in a position to do something about it. I think that Dr. Yudkin has understandable doubts about the practicability of this when he states that he does not suggest "that every doctor needs to be a psychiatrist or even 'psychiatrically orientated'". The general practitioner is usually not, nor should pretend to be, a psychiatrist; but I would go further and say that he should indeed be psychiatrically orientated, but not of course psychiatrically biased.

Physical and psychological disorders can and do exist together in varying degrees. Until the general practitioner becomes aware in consultation of a mother presenting him with a child as a symptom of her own trouble, he is unlikely to consider the question of what he might do to help.

What he might do, and indeed if he should do anything, about the deeper diagnosis are matters which are not relevant to this communication.

Leeds. NEVIL SILVERTON.

RETROBULBAR NEURITIS IN PERNICIOUS ANÆMIA

SIR,—The controversy between Dr. Matthews (June 10) and Dr. Smith (June 17) hinges on whether cyanide acts by converting hydroxocobalamin to cyanocobalamin or by splitting these substances off their carrier proteins. We are investigating the vitamin-B_{12}-binding capacity of serum by incubation with radioactive B_{12} followed by protein precipitation and estimation of the contained radioactivity.

For present purposes, the important finding is that addition of cyanide reduces the radioactivity of the precipitate to almost nil. This is difficult to explain on the basis of Dr. Smith's theory, for transfer from one binding protein to another should not affect the total radioactivity. Splitting of the B_{12} protein complex by cyanide, on the other hand, would be expected to produce such a result. Dr. Smith's objection that this explanation would presuppose binding of vitamin B_{12} in different proportions in "so-called normal people" loses its force in view of our experiments which seem to demonstrate just that.

And there is yet another possibility. If the binding of vitamin B_{12} to protein is an enzymatic process, as our results lead us to believe, cyanide could act by inhibiting the enzyme. This would again fit the findings outlined above. Our method is not, as yet, sufficiently delicate to distinguish clearly between this and Dr. Matthews' explanation.

Department of Medicine, University of Natal, Durban, South Africa. W. HIFT.

THIOPROPERAZINE

SIR,—Perrin et al.[1] found thioproperazine superior to the other phenothiazines they tested for treating maniacal attacks, delusional outbursts, and confusional states. We have given thioproperazine intravenously; outbursts of emotional, noisy, or violent behaviour can be very effectively treated by this means. The injections do not appear to be dangerous. There are few side-effects, and the only important side-effect we have seen was an urticarial reaction in 1 patient.

7·5 mg. (1 ampoule of 'Majeptil'), 15·0 mg., or 22·5 mg. was injected intravenously, diluted with sterile water to 7·5 ml. At first 7·5 mg. only was given, at the rate of about 1 mg. per minute; but, as there were no adverse reactions, later injections were completed in about twenty seconds. The patients' behaviour before and after injection, and blood-pressure and pulse-rate were recorded. We have so far given 22 patients 26 injections.

Psychopaths

We gave 7·5 or 15·0 mg. to 6 psychopaths of widely differing intelligence who had outbursts of violent and abusive behaviour. In each the mood altered dramatically ten to twenty minutes after the injection; and this persisted for twenty-four hours or more. They became calm, drowsy, and amenable to suggestion.

CASE 1.—An illegitimate woman of 47 who worked as a maid had been frequently admitted to mental hospitals. In hospital she worked in the ward; but she had episodes lasting several days with hysterical fits and violent "crushes" for female members of the staff. She was very violent and required heavy sedation. Three different phenothiazines, and chlordiazepoxide, phenobarbitone, and primidone (tried because of electroencephalographic dysrhythmia), failed to help her. Electroconvulsive therapy (E.C.T.) made her worse. 15 mg. thioproperazine was administered during a particularly violent attack. Fifteen minutes after the injection she became calm, stayed in bed without restraint, and drank tea. She slept for two hours, woke spontaneously for milk drink and toilet, and then slept again without sedatives. Next day she was tranquil and helpful in the ward.

Affective Psychotics

We have treated 4 cases, including 1 of involutional type. 1 had been admitted in mania; complete remission followed twenty minutes after an injection of 7·5 mg. 2 were chronic cases given 7·5, 15·0, and 22·5 mg. for sudden alterations of mood with aggressive, emotional behaviour; a calm, rational frame of mind was induced ten to thirty minutes afterwards. The 4th often had mania. 15·0 mg. given in a remission did not change her mood perceptibly.

CASE 2.—In a housewife of 50, married successfully for eighteen years to a farmer, a psychotic illness began at the menopause, marked initially by bizarre delusions and religious mania, and later by sudden severe depressive attacks. When well in hospital she is calm, cheerful, very helpful, and a notable knitter. E.C.T. controlled her mania or depression but did not prevent them. Chlorpromazine produced skin sensitivity; chlordiazepoxide and imipramine did not prevent depressive attacks. Thioproperazine cut short her attacks: agitation and weeping stopped in ten to twenty minutes. On different occasions 7·5, 15·0, and 22·5 mg. were given to study side-effects. The accompanying figure shows the sequence of events after giving 22·5 mg. In the induced state of calm, delusional material was discussed rationally and without affect.

Schizophrenics

7·5 or 15·0 mg. was given to 8 schizophrenics. In 4 chronic cases there was no improvement. A state of calm and drowsiness was induced in 2 patients admitted in mania, and in 1 chronic patient who had had a leucotomy and was violent. We were particularly impressed by the results in a catatonic.

CASE 3.—An orphaned 20-year-old of average intelligence and previously socially well-adjusted worked as a telegraph boy and postman. Seeking advancement, he took a correspondence course at which he did well, but unexpectedly failed the examination for clerk. He stopped work before Christmas, 1960, "because the work was too much". A week later he was admitted to this hospital, retarded, disoriented, and with aural and visual hallucinations. His attempts to answer questions usually failed and all his movements were slow. With prochlorperazine and 12 sessions of E.C.T. he remained mute. Misinterpreting the intentions of his attendants he would suddenly strike them. He had to be spoon-fed, and passed urine only during E.C.T. He was given 7·5 mg. of thioproperazine. Blood-pressure and pulse-rate were unaltered. About an hour after the injection he was obviously improved: he sat up and talked freely; he requested and ate a very large meal; he went to the toilet himself; and he watched television. Next morning he had relapsed; but 20 mg. of thioproperazine b.d. orally subsequently maintained him in remission.

Other conditions

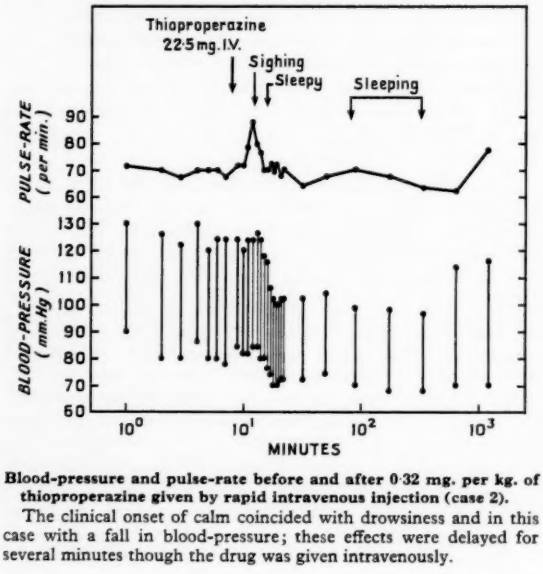
We have also treated 2 acutely confused patients. A paraphrenic woman of 60 suddenly became completely confused in the ward; her speech became incomprehensible. Thirty minutes after receiving 7·5 mg. thioproperazine she appeared improved, but she reverted to her former noisy state within an hour. The other was a woman of 74 with senile confusional psychosis of abrupt onset; injections of 7·5 and of 15·0 mg. thioproperazine calmed her after about thirty minutes; but this effect only lasted for about two hours.

No improvement was produced by 7·5 mg. in a woman of 50 with involutional depression, or by 22·5 mg. in a man of 44 with agitated depression.

Side-effects

Thioproperazine is a very potent tranquilliser which often rapidly produces extrapyramidal signs. These dominate the clinical picture when the drug is given by mouth for several days; but they were not prominent after intravenous injection. 2 patients had transient contortions of the facial muscles characteristic of the excitomotor crises caused by this drug[2] but there were no signs of parkinsonism. The accompanying table shows the effects observed and their time of appearance. It is interesting that the different subjective and objective effects followed at different intervals after injection: dryness of the mouth, and transient stimulation of pulse-rate and

1. Perrin, J., Lambert, P. A., Broussolle, P., Balvet, P., Beaujard, M., Revol, L., Achaintre, A., Berthier, C. N., Requet, A. *C.R. 56 Congr. Psychiat. Neurol. franç.* 1958, p. 794.



Blood-pressure and pulse-rate before and after 0·32 mg. per kg. of thioproperazine given by rapid intravenous injection (case 2).

The clinical onset of calm coincided with drowsiness and in this case with a fall in blood-pressure; these effects were delayed for several minutes though the drug was given intravenously.

2. Delay, J., Deniker, P., Ropert, R., Barande, R., Eurieult, M. *Ann. méd-psychol.* 1959, **116**, 600.

EFFECTS OF INTRAVENOUS THIOPROPERAZINE

Effect	Frequency	Time of onset (min. after injection)
Dry mouth	3/26	1–5
Tachycardia	3/13	2, 3 (and 20 with urticaria)
Sighing	4/26	2–10
Tremor	2/26	5–10
Blood-pressure drop	2/13	7, 8
Calm	15/17	5–45 (av. 17·5)
Drowsiness	9/26	5–45 (av. 20)
Urticaria	1/26	20 (lasted 60)
Increased appetite	2/26	30
Excito-motor signs:		
Eye	1/26	60 (transient)
Jaw	1/26	120 (given promethazine)
Blurred vision	1/26	12 hr.

respiration preceded the onset of calm, usually accompanied by drowsiness. None of our patients had the extreme tachycardia described in 1 case by Coirault et al.[3] Extrapyramidal effects (2 patients) were not seen until one or two hours after injection. Although blood-pressure fell in 2 patients, the drop was not serious in either (see figure for the readings in the more severe case). The only serious side-effect was urticaria coming on twenty minutes after injection of 22·5 mg. and persisting for about one hour. It cleared without treatment.

Even when the drug is given intravenously many of its effects, including the therapeutic calming effect, do not appear for some time.

There was a striking improvement, irrespective of the diagnosis, in patients in acute emotional states. Weeping, depressed patients, excited hallucinated patients, and patients with violent emotional outbursts did well. But the behaviour of chronic schizophrenics and other apathetic patients did not change.

The appearance of the various effects at different times after intravenous injection of thioproperazine suggests that the drug has several sites of action, some of which are reached before others.

We wish to thank the physician-superintendent, Dr. A. M. Wyllie, for allowing us to carry out this trial, and May & Baker, Ltd., for supplies of 'Majeptil' and for English translations of papers read at the 56th Congress of Psychiatrists and Neurologists in Strasbourg, July, 1958, of which summaries were published in the *Annales médico-psychologiques*.

Royal Aberdeen Mental Hospital.

ELIZABETH LUKE
J. H. WYLLIE.

SURVIVAL OF MICROFILARIA BANCROFTI IN STORED BLOOD

SIR,—Disturbance of the erythrocytes, observed when crossmatching blood, led to the detection of vigorously lashing microfilariæ in the erythrocyte/serum mixture. Investigation revealed that the prospective donor's blood was teeming with them; and they were identified as *Microfilaria bancrofti*.

This blood, collected in anticoagulant acid-citrate/dextrose solution, had been stored in the blood bank at 4–6°C for 12 days; its appearance was normal. It had been taken from an apparently healthy donor who had been subjected to the usual screening tests [4]; but it is well known that often the presence of adult filariæ in the body (confirmed by finding microfilariæ in the blood) is not associated with recognisable clinical features.

Transfusion of blood containing microfilariæ does not transmit filariasis (the mosquito vector is essential), and no other ill effects have followed the deliberate transfusion of fresh blood containing microfilariaæ,[5] We withdrew the blood from the bank, however, because we feared that degradation products of dead microfilariæ might produce either a febrile or a sensitive reaction in the recipient. The blood was segregated and kept at 4–6°C, and wet films were examined from time to time. On the 21st day after collection the microfilariæ were inactive at 4°C, but were revived by warming the slide to 37°C. On the 25th day they could not be revived at 37°C.

Strong [5] states that Hinman found that the microfilariæ of *Dirofilaria immitis* survived in vitro, in citrated blood, for 10 days at 39°C. We do not know of any reports on the survival of *Microfilaria bancrofti*, or other microfilariæ, at blood-bank temperatures. The survival of microfilariæ under these conditions suggests a convenient means of preserving them for at least 24 days for teaching purposes.

It is interesting to compare the survival-times, in bank blood, of other important contaminants. Bacteria and viruses survive indefinitely, *Treponema pallidum* for not longer than 72 hours,[4] *Plasmodium malariæ* for " weeks ",[6] and *Plasmodium falciparum* for at least 14 days.[7]

Blood Transfusion Department, Armed Forces Medical College, Poona, India.

G. W. G. BIRD
K. K. MENON.

ADVERTISEMENTS FOR HEALTH

SIR,—In her article last week, Dr. Mullins makes " a plea for truth " which seems to justify the comment that she thinks " all the world (of advertising) is a bit queer ". If one can narrow down her arguments, they appear so patently one-sided that they may well defeat her object. She quotes, for example, the need for truth, the whole truth, and nothing but the truth in advertising; that surely is a policy of perfection which even the medical profession is unable to adhere to.

While one may accept the fact that a proportion of the public is gullible, and that a limited number of pharmaceutical advertisers may take advantage of this fact, Dr. Mullins' wholesale condemnation of their advertisements for health overlooks the fact that some, at least, of this advertising saves the doctor from an unnecessary flood of N.H.S. patients. Be that as it may, Dr. Mullins blanket attack on advertising in medical journals strikes one as being distinctly harsh.

This Company is responsible for a fair proportion of such advertising, and many of our clients agree with us that continual care and restraint are required in their approach to doctors. In other words, that their presentation should be, as far as possible, impeccable.

Dr. Mullins seems to make little allowance for those ethical pharmaceutical houses which make it their business to respect the needs of the medical profession in this matter.

General Advertising Company of London, London, W.C.2. MAURICE KEATING.

INDUSTRY AND PROFESSION

SIR,—Dr. Bradshaw's suggestions last week can only increase the widespread unease about the relationship between the medical profession and the pharmaceutical industry. He urges a very much wider cooperation by means of " a formal acknowledged union " that is " staunch, friendly, and normally permanent ", of each large pharmaceutical firm and perhaps several small ones too, with one medical school. In return for some of the profits, the medical school would try to give priority to trials of the firm's new products and would " raise a deprecatory and respected hand in the face of any promotional excesses ". By this system he thinks the " integrity of the profession " would flourish along with the drug firms.

3. Coirault, R., Girard, V., Jarret, R., Rouif, J. *ibid.* 1959, **117**, 45.
4. Mollison, P. L. Blood Transfusion in Clinical Medicine. Oxford, 1956.
5. Strong, R. F. Stitt's Diagnosis, Prevention, and Treatment of Tropical Diseases. London, 1945.
6. Hutton, E. L., Shute, P. G. *J. trop. Med. (Hyg.)* 1939, **42**, 309.
7. Grant, D. B., Perinpanayagam, M. S., Shute, P. G., Zeitlin, R. A. *Lancet*, 1960, ii, 469.

If education is important in directing people in the way you want them to go, Dr. Bradshaw is advocating the perfect set-up for promoting the sale of drugs. The education of medical students would be harnessed to the drug industry, whose (in Dr. Bradshaw's own words) " raison-d'être in a free economy *is* to make profits ". Despite the obvious advantages to both sides, it is difficult to see how such an arrangement could fail to distort medical truth, which is, after all, the raison-d'être of medical education. It is perhaps significant that on the very same page of *The Lancet* as Dr. Bradshaw's letter, another defender of pharmaceutical persuaders states that in his view there is no such thing as " straightforward information ", and quotes Taplin's remark " that anyone who suggests that advertising can in practice be a matter of information only is talking nonsense ".

But Dr. Bradshaw goes further. If his suggestions are adopted, not only medical students but also the public can be educated from an early age in the way that they should go. What would a firm's shareholders say, asks Dr. Bradshaw, when they saw some of its profits being milked away to equip a new pædiatric unit? " They would swallow hard at first, but they would soon be applauding the increased flow of valuable new drugs." Presumably the little pædiatric patients could at the same time be educated in the benefits of growing up with the aid of these valuable new drugs. We could then have infinite extensions of Dr. Bradshaw's alliterative suggestions. The mind boggles at the thought of drug warfare, with gaudy literature in the letter-box; " Guy's for gallstones ", counterblasted by " Belfast for bile ducts ", and " Livers live longer at The London ".

London, S.E.21. ANN MULLINS.

SERUM-HAPTOGLOBINS IN CHILDHOOD

SIR,—The term " haptoglobin " was introduced by Polonovski and Jayle [1] to describe a group of serum-mucoproteins specifically capable of binding hæmoglobin in vivo and in vitro and of forming complexes with it.[2 3] Smithies [4] showed by electrophoresis in starch-gel that normal sera contain three types of haptoglobins, which are now known to occur in three genetically controlled combinations (types 1–1, 1–2, and 2–2).

Normal serum-haptoglobin level is 40 to 150 mg. per 100 ml. Haptoglobins cannot be demonstrated in cord blood or in the early neonatal period.[5 6] An increased content of haptoglobin has been found in a variety of disorders associated with inflammation or tissue destruction. On the other hand, a lowered concentration or complete absence of haptoglobins has been reported in liver-cell failure,[3 7] pernicious anæmia,[8–11] and various types of hæmolytic anæmia.[5 9 12 13]

In an attempt to determine the normal values of serum-haptoglobins in children, we studied 305 normal infants and children aged between 20 days and 14 years. Serum-haptoglobins were measured by a colorimetric method based on the peroxidase activity of the haptoglobin/methæmoglobin complex.[14] Serum from 30 healthy adults was used to determine the normal serum-haptoglobin range. A mean value of 98±30 mg. per 100 ml. was obtained.

Our results, summarised in the accompanying table, show that haptoglobin concentration in healthy children is independent of age. We were not able to demonstrate haptoglobins in 10 samples of umbilical blood from full-term newborns.

MEAN VALUE OF SERUM-HAPTOGLOBINS AT VARIOUS AGES

Age (yr.)	No. of persons	Mean value of haptoglobin (mg. per 100 ml.)
20/365—1	120	97
2	20	100
3	16	109
4	13	91
5	13	89
6	14	96
7	13	92
8	14	104
9	19	92
10	14	110
11	16	101
12	10	81
13	10	110
14	13	93
Adults	30	98
Total and overall mean	335	97

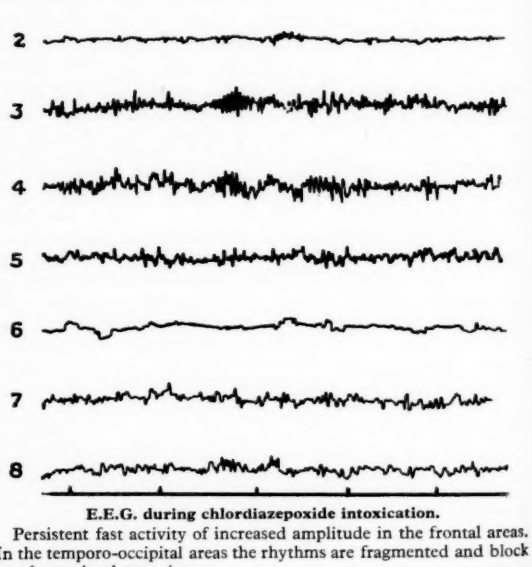
Pædiatric Clinic, Ahepa Hospital, Salonica, Greece. S. SKLAVUNU-ZURUKZOGLU K. MALAKA.

A LARGE OVERDOSE OF CHLORDIAZEPOXIDE

SIR,—We were interested to read the report by Dr. Jenner and Dr. Parkin (Aug. 5) of an overdose of chlordiazepoxide. We note that electroencephalographic (E.E.G.) tracings before and thirty-six hours after the drug intoxication were normal.

A patient had taken 19 capsules of chlordiazepoxide ('Librium') (190 mg.) as a suicidal gesture. Though this amount is modest and even within the therapeutic range, she had an abnormal E.E.G. during the period of intoxication. Her state of consciousness twelve hours after ingesting the capsules was one of drowsy indifference; but she was rapidly aroused by conversation. The blood-level of chlordiazepoxide obtained by a modified sulphonamide-type analysis [1] was then 5·3 mg. per

1. Bratton, A. C., Marshall, E. K., Jr. *Quart. J. Pharm.* 1939, **12**, 4.



E.E.G. during chlordiazepoxide intoxication.

Persistent fast activity of increased amplitude in the frontal areas. In the temporo-occipital areas the rhythms are fragmented and block poorly to visual attention.

Leads: 1. rt. inferior frontal; 2. rt. superior frontal; 3. lt. superior frontal; 4. lt. inferior frontal; 5. rt. temporo-occipital; 6. rt. parieto-occipital; 7. lt. parieto-occipital: 8. lt. temporo-occipital.

1. Polonovski, M., Jayle, M. F. *C.R. Acad. Sci., Paris*, 1940, **211**, 517.
2. Jayle, M. F. Thesis, Paris, 1939.
3. Jayle, M. F., Boussier, G. *Expos. ann. Biochim. méd.* 1955, **17**, 157.
4. Smithies, O. *Biochem. J.* 1955, **61**, 629.
5. Allison, A. C., ap Rees, W. *Brit. med. J.* 1957, ii, 1137.
6. Tuttle, A. H. *Science*, 1955, **121**, 701.
7. Nyman, M. *Scand. J. clin. Lab. Invest.* 1959, **11**, suppl. 39, p. 1.
8. Allison, A. C. *Proc. R. Soc. Med.* 1958, **51**, 641.
9. Neale, F. C., Aber. G. M., Northam, B. E. *J. clin. Path.* 1958, **11**, 206.
10. Nyman, M. *Scand. J. clin. Lab. Invest.* 1957, **9**, 168.
11. Owen, J. A., Carew, J. P., Cowling, D. C., Hoban, J. P., Smith, H. *Brit. J. Hæmat.* 1960, **6**, 242.
12. Mehta, R. S., Jensen, N. W. *ibid.* p. 250.
13. Nosslin, B. F., Nyman, M. *Lancet*, 1958, i, 1000.
14. Owen, J. A., Better, F. C., Hoban, J. *J. clin. Path.* 1960, **13**, 163.

ml.; but an unexpected abnormal E.E.G. was obtained showing fast activity typical of barbiturate intoxication (see figure). Three days later, the E.E.G. had reverted to normal. The patient's subsequent progress was satisfactory. The results of liver-function tests and a blood-count were normal.

The changes in the E.E.G. are similar to those in barbiturate intoxication; but a rapid recovery from drowsiness is never seen with barbiturates. As far as we know, E.E.G. abnormalities associated with chlorodiazepoxide intoxication have so far been described only in the United States by Randall.[2]

Western Infirmary, Glasgow.
J. THOMSON
A. I. M. GLEN.

MODERN DEVELOPMENTS IN LIVER SURGERY

SIR,—I have read with great interest the Occasional Survey by Mr. Brearley.[3] The only thing I regret is that he did not mention the important contribution to the subject made by the staff of the Municipal Hospital at Arnhem, the Netherlands.[4–6]

Experimental work on the regenerative power of the liver has led these clinicians to design an operative procedure (" Schalm's operation ": ligation of one of the hepatic bile-ducts) which might be of value in treating liver cirrhosis. A limited number of patients have already been operated upon. Dr. Bax and Dr. Schalm have travelled to South Africa in order to discuss the possibilities of this treatment in the Bantu among whom cirrhosis of the liver is notoriously common.

University Hospital, Utrecht, The Netherlands.
F. DE WAARD.

MUSHROOM POISONING

SIR,—The article on mushroom poisoning by Dr. Elliott and others (Sept. 16) ended with a recommendation that made me a little sad. This was to avoid fungi growing near trees or those with a volva. If one follows this rule one will miss two of the best edible fungi: *Amanita rubescens* (the Blusher) and *Russula cyanoxantha*.

A. rubescens may be distinguished from its lethal cousin by the fact that the cut surface of the cap and stem turns a brownish red on exposure to the air. *R. cyanoxantha* cannot be confused with *R. emetica*, which has a bright red cap, but needs to be distinguished from certain inedible species of the genus Lactaria. The latter give off a white milky fluid, when broken, which tastes peppery.

Most of the other really good edible fungi grow in the open. I particularly recommend *Lepiota rachodes* (a near relative of *L. procera*, the parasol mushroom, also edible), *Clitocybe nebularis*, *Tricholoma nudum* and its relative *T. personatum*, both Blewits, and *Lactaria deliciosa*, which is yellow and rather like a Chantarelle. Members of the Boletus genus, with their tubular gills, are much recommended, but with the exception of *B. edulis* their flavour leaves much to be desired. Besides one has to avoid *B. satanus*, the flesh of which turns blue on exposure to the air. So it does with some other species, but it is a useful guide, and the change does not occur in the good ones.

Perhaps I should add that before eating an unfamiliar fungus I always get it identified by a competent mycologist.

Department of Pathology, University of Bristol.
OLIVER C. LLOYD.

SIR,—The excellent article on mushroom poisoning contains what I take to be a few errors.

The diagram of the fungus concerned is misleading because although *Amanita phalloides* may retain part of the volva adherent to the cap, it does not do so characteristically, and indeed the drawing is more suggestive of *A. mappa*. Surely volva and ring are found also in the genus Annelaria. Although, very possibly, healthy people do not often succumb to other forms of poisoning by fungi, apparently well-authenticated deaths have occurred from *Entoloma lividum* and *Inocybe patouillardi*, and if eaten raw *Helvella* (*Gyromitra*) *esculenta* has proved fatal. Although Neuhann's remarks about the significance of psychological symptoms are worth quoting, death does not invariably follow their appearance.

De La Pole Hospital, Willerby, Hull.
J. A. R. BICKFORD.

PROPERTIES OF X CHROMOSOMES

SIR,—The attractive hypothesis formulated by Lyon [1] to explain the ambiguous behaviour of X-linked recessive genes in heterozygous female mice was introduced in this journal by Polani and Hamerton [2] who were considering the phenotypic expression in man of the X-linked recessive gene responsible for colour-blindness. Lyon contends that an individual X chromosome which remains heavily condensed during somatic interphase is restrained from exerting any genic influence. Since in mammals one of the two Xs in the female somatic cell always forms the sex-chromatin body,[3] only one X chromosome in both female and male cells is actually functioning.

In *Drosophila melanogaster*, the X chromosome is composed of two distinct areas. The euchromatic region containing most of the genetic factors invariably remains in an extended state, while the heterochromatic region condenses to form a chromocentre at somatic interphase in both sexes.[4] In man and other mammals, quite another situation exists. The X chromosome is not made of two regions; rather, each X chromosome behaves differently from its homologue. Thus, an entire X, when heteropyknotic, forms the sex-chromatin body (see figure); when isopyknotic, the X is indistinguishable from the euchromatic autosomes.[3 5] Because of this remarkable disparity in the properties of the X chromosome, analogies between *drosophila* and man, at least so far as X-linked traits are concerned, may be hard to find. Lyon's hypothesis has taken into account this ambivalent behaviour of mammalian X chromosomes and provided us with a new insight into several situations in man.

The normal male is naturally monosomic for the X, and the

1. Lyon, M. F. *Nature, Lond.* 1961, **190**, 372.
2. Polani, P. E., Hamerton, J. L. *Lancet*, July 29, 1961, p. 262.
3. Ohno, S., Makino, S. *ibid.* 1961, i, 78.
4. Kaufmann, B. F. *J. Morphol.* 1934, **56**, 125.
5. Ohno, S., Weiler, C. *Chromosoma (Berl.)* 1961, **12**, 362.

A somatic cell in mid-prophase from a 4-month-old female fœtus containing one chromosome precociously condensed along its entire length, presumed to be an X.

2. Randall, L. O. *Dis. nerv. Syst.* 1959. **21**, suppl. 3, p. 7.
3. Brearley, R. *Lancet*, 1961, i, 935.
4. Schalm, L., Schulte, M. J., Miete, M., Bax, H. R., Mansens, B. J., Rodrigues Pereira, A. *ibid.* 1952, i, 75.
5. Schalm, L., Bax. H. R., Mansens, B. J. *Gastroenterology*, 1956, **31**, 131.
6. Bax, H. R. *Arch. chir. neerl.* 1956, **8**, 331.

XO-female can reach maturity in reasonably good health. On the other hand, monosomy for autosomes is almost uniformly lethal; even trisomic conditions seem to be lethal or semi-lethal, unless the autosome involved is very small—i.e., chromosomes 21 or 22. At any rate, trisomy for the X is much less detrimental to an individual than trisomy for chromosome 21. Possibly the X is so highly specialised as a female-determiner that despite its large size, it contains fewer genetic factors than the smallest autosome, although the great number of X-linked hereditary traits known in man does not support this assumption. The fact that even the XXXY constitution gives rise to a phenotypic male has been taken as evidence in favour of the small Y possessing great male-determining capacities. If the X then is such a weak female-determiner, how does it differ from autosomes of a similar size?

On the basis of Lyon's hypothesis, one might postulate the presence of a built-in buffer mechanism which inactivates all X chromosomes additional to the basic formula of 2AX. In the presence of a diploid set of autosomes, 2A, the maximum number of sex-chromatin bodies seen at somatic interphase usually equals the number of X chromosomes present minus one.[6] No matter how many Xs are present, only one appears to be active. Monosomy, trisomy, or even tetrasomy have very little functional effect; to all intents and purposes, the Y confronts one X.

Department of Experimental Pathology,
City of Hope Medical Center,
Duarte, California.

SUSUMU OHNO.

MENTAL DEFICIENCY AND ABERRANT SEX CHROMATIN

SIR,—Since the discovery of sex chromatin in 1949,[7] several surveys of the frequency of abnormalities of nuclear sex have been made, mainly in newborn infants and mental defectives.

The incidence of Klinefelter's syndrome with a positive sex-chromatin pattern in newborn male infants is about 0·3% [8] and in institutions or schools for male mental defectives about 1%.[9 10] The incidence of chromatin-negative females at birth is about 0·03% [9] and among educationally subnormals about 0·4%.[11] The incidence of newborn females with two sex-chromatin bodies and a XXX-chromosome constitution is about 0·13%[9]. XXX females make up 0·7% of mentally retarded women in institutions.[12]

Sex-chromatin aberrations thus occur more frequently among mental defectives than among normal individuals. All reported studies on the mentally deficient have been based on samples gathered in institutions or schools for mental defectives. Since it is probable that at least the Klinefelter syndrome may be associated with mental retardation of only a slight degree,[13 14] we can expect that only a small proportion of such cases would be admitted to institutions.

Our material is not extensive; but it is drawn from a general population.

In a Southern Swedish population of 7533 persons, 132 mental defectives were found in a detailed population study.[15] In this study those who had I.Q. scores below 68 (corresponding to −2 standard deviations) on the Stanford-Binet revised form were classified as mental defectives.

The sex-chromatin pattern was determined by the buccal-smear technique.[16] In the 88 defectives investigated, no case of aberrant sex chromatin was found (see accompanying table).

NUMBER OF MENTAL DEFECTIVES INVESTIGATED

Grade	In institutions		Not in institutions		Total	
	M	F	M	F	M	F
Feeble-minded ..	3	5	28	16	31	21
Imbeciles	9	8	7	5	16	13
Idiots	1	5	0	1	1	6
Total	31		57		88	

We therefore suggest that sex-chromatin aberrations associated with this degree of mental deficiency are very uncommon in a general population. Probably sex-chromatin aberration is more frequently associated with a slighter degree of mental retardation and thus most often found among subnormals (i.e., those patients with I.Q.s in the range 85–70 [approximately −1 to −2 standard deviations]).

Institute of Medical Genetics,
University of Uppsala, Sweden.

K.-H. GUSTAVSON
H. O. ÅKESSON.

DIAGNOSIS OF MALIGNANCY BY CHROMOSOME COUNTS

SIR,—Determining the origin of cells in pleural and peritoneal fluids is often very difficult because of the range of variation of mesothelial cells. An adaptation of new chromosome techniques has permitted a more positive approach.

The chromosomal constitution of malignant tumours can be studied directly since malignant tissue is actively dividing. The cells rarely, if ever, contain the normal number of 46 chromosomes and the number usually differs widely from this. There is a variation from cell to cell, but the counts can usually be plotted to show one or more modal frequencies or stem lines. Chromosomes in normal body cells, even when the latter are actively stimulated, do not depart significantly from the number of 46 and are consistent from cell to cell, even if the number is abnormal. If, therefore, cells of unknown origin are studied in mitosis, it is possible to infer whether or not they are of malignant origin from the pattern of the chromosome counts.

This principle has recently been applied to the study of pleural fluids. A few millilitres of the fluid are collected into about 10 ml. of water containing a small amount of heparin, and colchicine to a final concentration of about 0·003%. After half an hour, the cells are very gently spun down, and then fixed and prepared by the method of Moorhead et al.[1] The slides are scanned for metaphase plates, and the chromosomes in these counted under oil immersion. If no metaphase plates are found, no conclusions can be drawn, but in this case it is improbable that direct morphological examination of the cells will lead to any difficulties. If collections of 46 chromosomes (or something very close to it) are found, then it is assumed that these are dividing non-malignant body cells. If chromosome counts vary from cell to cell and the modal frequency is something other than 46, then the probability of malignancy is high. It is, of course, possible in some instances that the dividing cells will be a mixed population, but the counts should show this quite clearly.

The method is more time-consuming than the usual ones; but the time spent is not disproportionate to the advantages of reaching a firm diagnosis in selected cases. Other specimens have not yet been studied in this way; but the method could be used whenever mitotic activity continues after exfoliation.

Royal Women's Hospital,
Melbourne,
Victoria,
Australia.

GILLIAN F. JACOB.

6. Barr, M. L., Carr, D. H. *Canad. med. Ass. J.* 1960, **83**, 979.
7. Barr, M. L., Bertram, E. G. *Nature, Lond.* 1949, **163**, 676.
8. Maclean, N., Harnden, D. G., Brown, W. M. *Lancet*, Aug. 19, 1961, p. 406.
9. Mosier, D., Scott, L. W., Cotter, L. H. *Pediatrics*, 1960, **26**, 291.
10. Ferguson-Smith, M. A., Johnston, A. W., Handmaker, S. D. *Lancet*, 1960, ii, 184.
11. De La Chapelle, A., Hortling, H. *Nord. med.* 1960, **9**, 256.
12. Fraser, J. H., Campbell, J., MacGillivray, R. C., Boyd, E., Lennox, B. *Lancet*, 1960, ii, 626.
13. Pasqualini, R. Q., Vidal, G., Bur, G. E. *ibid.* 1957, ii, 164.
14. Shapiro, A., Ridler, M. A. C. *J. ment. Defic. Res.* 1960, **4**, 48.
15. Åkesson, H. O. (in the press).
16. Klinger, H. P., Ludwig, K. S. *Stain Tech.* 1957, **32**, 235.

1. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., Hungerford, D. A. *Exp. Cell Res.* 1960, **20**, 613.

MYELOMATOSIS

SIR,—We read with great interest the papers by Professor Martin,[1] Dr. Innes and Dr. Newall,[2] and Professor Waldenström and his colleagues.[3] We have studied the incidence, age, and sex distribution of multiple myeloma in different ethnic groups in Israel.

No significant differences between Jews born in Africa and Asia on the one hand and those born in Europe and America on the other were observed. The frequency per 100,000 of myeloma for the years 1956–60 was found to be 4·69 for the European-American-born group and 3·65 for the Asian-African group.

The data on age and sex distribution of multiple myeloma in Israel are as follows:

30–40		*40–50*		*50–60*		*60–70*		*70–80*		*Total*	
M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
5	6	21	10	21	22	21	27	14	12	82	77
11		31		43		48		26			

Most of the cases occurred between the ages of fifty and seventy. The data are similar to Martin's and differ from Waldenström's.

The sex distribution in our series is closer to that described by Waldenström. A detailed report on this series will be published in the near future.

We wish to thank the heads of medical departments in this country for cooperating in this investigation and also Dr. G. Kellner, of the Israeli Bureau of Statistics, for guidance. This study was supported by the Hematology Research Foundation, Washington, U.S.A.

Department of Hæmatology, Government Hospital, Tel-Hashomer, Israel.

B. RAMOT
M. SALOMI.

UNHYGIENIC TELEPHONE KIOSKS

SIR,—Anyone who is forced to make frequent use of public telephone kiosks must feel nauseated by the appalling state of neglect in which many of them are to be found. One gets the impression that they are never disinfected and the receivers are often so filthy that it is impossible to imagine them ever having been cleaned. When one realises how many members of the public use these kiosks each day, the danger of contamination of infectious diseases from the ear and mouth pieces is considerable.

It is time the Postmaster-General organised a much greater supervision of the thorough cleansing of these kiosks, for I feel sure that their disgraceful condition could become a serious menace to the health of the population.

London, W.1. MAX ODENS.

Obituary

RICHARD M. L. MASON

AT the beginning of this month Richard Mason was killed by Indians in Brazil. Educated at Lancing and Magdalen College, Oxford, he would have qualified at St. Thomas's Hospital next year.

A. L. C. writes: "From every generation there springs a very small minority who become dedicated to some pursuit, often of a hazardous nature, which is outside the main channel of their ultimate aim in life. In some subtle way without ever seeking prominence they contribute much to the leadership of their generation and help to guide it from the clutches of the utterly orthodox. Richard Mason at 26, already the recipient of a Royal Geographical Society medal and leading his second expedition in South America, was one of these. We mourn his loss as a young man of outstanding ability, great modesty, and much charm of character."

1. Martin, N. H. *Lancet*, 1961, i, 237.
2. Innes, J., Newall, J. *ibid.* p. 239.
3. Waldenström, J., Paraskevas, F., Heremans, J. *ibid.* p. 1147.

Notes and News

CONTROL OF DRUGS

SPEAKING at the opening of the British Pharmaceutical Conference in Portsmouth on Sept. 15, Dr. D. C. Garratt, chairman of the Pharmaceutical Society, said that the control of drugs was inadequate and that a change of legislation or procedure was desirable for the protection of the public. He proposed that the control of drugs should be taken out of the Food and Drugs Act and incorporated in a new Medical Substances and Preparations Act built around sections 11, 12, and 13 of the Pharmacy and Medicines Act. Legal status should be given to the standards of the *B.P.* and *B.P.C.* and to officially recognised standards of other drugs. The Pharmaceutical Society had already recommended that the control of medicines should be separated from that of other substances and vested in the Ministry of Health. Dr. Garratt also considered that, as a safeguard against the importation of inferior drugs, no imported consignments should be sold or used unless they carry a certificate of purity from a recognised laboratory in this country.

CRUDE DRUGS

A NEW journal devoted to crude-drug research [1] is published in English, French, and German. In the first issue an introductory article claims that "crude botanical drugs and their galenical preparations should be used in preference to chemically isolated ingredients or synthetics". This issue contains short reviews of six different plants and the medicinal uses of preparations derived from them.

ACTA NEUROPATHOLOGICA

THE Commissions for Neuropathology and Comparative Neuropathology of the World Federation of Neurology are to publish this journal at indefinite intervals. Prof. F. Seitelberger of Vienna is the editor and Prof. William Blackwood of London is one of the editorial board. It is the aim of the board to offer an opportunity for a broad international exchange of ideas in the "ever more complex field of the neurological sciences". To this end they are prepared to publish papers in German, English, or French.

The first number [2] includes an account by H. Hager of the fine structure of the walls of the cerebral blood-vessels as revealed by electronmicroscopy, the capillaries of the brain being compared with those of other organs, and a report by L. E. Farr and colleagues of neutron-capture therapy of a cerebellar sarcoma resistant to X radiation in which the brain and tumour exposure to thermal neutrons was far greater than previously recorded. The tumour was thought to originate in the vascular sheath, chiefly around vessels in the granular layer.

Royal Faculty of Physicians and Surgeons of Glasgow

Dr. A. S. Parkes will give a Burns lecture on Monday, Oct. 2, at 5.15 P.M., at the Faculty, 242, St. Vincent Street, Glasgow. He will speak on the preservation and grafting of gonadal tissue.

Harveian Society of London

Buckston Browne Prize.—The subject chosen for the next competition for this prize is De Motu Cordis. The prize is open to any doctor registered in Britain or the Dominions who is under 45 years of age. Essays must be sent by Aug. 31, 1962, to the hon. secretaries of the society, 11, Chandos Street, W.1.

College of General Practitioners

On Sunday, Nov. 26, a symposium on the training of the family doctor for his work in the community, sponsored by the Wellcome Foundation, will be held at the Wellcome Building, Euston Road, London, N.W.1. Registration fees (15*s.*) should be sent to the secretary of the college, 41, Cadogan Gardens, London, S.W.3.

1. *Quarterly Journal of Crude Drug Research*, 1961, vol. 1, no. 1. Published by Dr. E. F. Steinmetz, 347, Keizersgracht, Amsterdam, Netherlands. 49*s.* 6*d.* per annum.
2. Springer-Verlag, Berlin-Wilmersdorf, Heidelberger Platz 3. D.M. 38.

Institute of Laryngology and Otology

On Friday, Sept. 29, at 3.30 P.M., at the institute, 330, Gray's Inn Road, London, W.C.1, Mr. A. S. Walker will speak on the application of hearing-aids.

Institute of Obstetrics and Gynæcology

On Tuesday, Sept. 26, at 2 P.M., at the Chelsea Hospital for Women, Dovehouse Street, London, S.W.3, Prof. D. B. Stewart of the University College of the West Indies will speak on organisation of obstetric and gynæcological services in underdeveloped countries. On Friday, Sept. 29, at 9.45 A.M., at Queen Charlotte's Hospital, Goldhawk Road, W.6, Prof. Denis Hill will give a lecture on puerperal insanity, and at 3 P.M. Mr. C. W. F. Burnett and Mr. R. Lloyd Jones will discuss eclampsia. Tickets for these lectures may be had from the secretary of the institute, Chelsea Hospital for Women.

Liverpool Society of Anæsthetists

The first meeting of the 1961–62 session of this society will be held on Friday, Oct. 13, at 8 P.M., at the Liverpool Medical Institution, when Prof. T. C. Gray will give an address entitled Some Highlights and Impressions of my Tour. Other speakers during the session will include Dr. W. D. Wylie and Prof. W. D. M. Paton. The hon. secretary of the society is Dr. E. S. N. Fenton, 2, Lancaster Avenue, Liverpool, 17.

National Association for Mental Health

A residential weekend course on psychiatry for the general practitioner is to be held by this Association from Nov. 17 to 19 at the Waverley Hotel, Southampton Row, London, W.C.1. The cost of the course, including residence and tuition, is £12 12*s.* 6*d.* Application forms may be had from the education secretary of the Association, 39, Queen Anne Street, W.1.

The Health Visitor and the Family Doctor

A symposium on this subject, organised by the Royal College of Nursing, the College of General Practitioners, and the Society of Medical Officers of Health, is to be held on Saturday, Oct. 28, at 10 A.M., at the Wellcome Building, Euston Road, London, N.W.1. The medical speakers will include Dr. G. E. Godber, Dr. George Swift, Dr. I. A. G. MacQueen, Prof. R. C. Wofinden, and Dr. Richard Scott. Tickets (10*s.* 6*d.*) may be had only by members from the colleges and the society.

International Congress of Internal Medicine

This congress will take place in Munich from Sept. 5 to 8, 1962, under the chairmanship of Prof. E. Wollheim. The programme includes discussions on: immunity processes in the pathogenesis of internal diseases; shock and collapse in internal medicine; and environment and disease. Further particulars may be had from the secretary of the congress, Schwalbacherstrasse 62, Wiesbaden, German Federal Republic.

Medical World Conference

A conference on general practice is to be held by the *Medical World* on Sunday, Oct. 22, at Victoria Halls, Bloomsbury Square, London, W.C.1. Subjects for discussion will be the general practitioner's relations with the hospitals, the Ministry of Health, the pharmacist, and the health visitor. The chairman of the conference will be Dr. J. A. Scott and the speakers will include Dr. W. S. Macdonald and Dr. C. E. Gallagher. Tickets may be had from the *Medical World*, 56, Russell Square, W.C.1.

Methods of Resuscitation

The St. John and the St. Andrew's Ambulance Associations and the British Red Cross Society have approved the use of the expired-air method and external cardiac massage for first-aid resuscitation.

Professional Nurses and Midwives Conference and London Nursing Exhibition

This conference and exhibition will be held, under the auspices of the *Nursing Mirror*, from Oct. 16 to 20, at Seymour Hall, London, W.1. Details may be had from the organiser of the exhibition, Dorset House, Stamford Street, S.E.1.

Queen's Institute of District Nursing

The annual meeting of this Institute will be held at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, on Thursday, Oct. 19, at 2.30 P.M., when Mr. Enoch Powell, the Minister of Health, will address the meeting.

Agricultural Problems in Developing Countries

The Nutrition Society is to hold a symposium on this subject on Friday, Oct. 13, at 10.45 A.M., at the National Institute for Research in Dairying, Shinfield, Reading. Further particulars may be had from the hon. programmes secretary of the society, Miss D. F. Hollingsworth, c/o Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, London, S.W.1.

Mr. H. J. Seddon will give the inaugural address to the Royal Free Hospital School of Medicine on Wednesday, Oct. 4, at 3 P.M. at Senate House, London, W.C.1.

A weekend course in psychiatry is to be held at St. John's Hospital, Stone, Bucks, on Sept. 30 to Oct. 1. The speakers will include Dr. W. W. Sargant, Dr. J. S. I. Skottowe, Dr. J. A. Oddie, Dr. C. A. H. Watts, and Dr. D. C. Watt.

The annual dinner of past and present students of the Leeds School of Medicine will be held on Friday, Oct. 20, when the guest of honour will be Mr. A. Dickson Wright.

The autumn dinner of the Wessex Rahere Club will take place on Saturday, Oct. 28, at the Lansdown Grove Hotel, Bath, under the chairmanship of Dr. Pascoe Hill. The hon. secretary is Mr. A. Daunt Bateman, 11, The Circus, Bath.

Copies of the National Health Service (Superannuation) Regulations 1961 (S.I. 1961, no. 1441), which consolidate with amendments the regulations of 1955, 1958, and 1960, may be had from H. M. Stationery Office (3*s.* 6*d.*). The new regulations come into force on Oct. 1.

Appointments

BOURNE, G. L., F.R.C.S., M.R.C.O.G.: consultant, department of obstetrics and gynæcology, St. Bartholomew's Hospital, London.
CROWCROFT, ANDREW, M.B. Lond., D.P.M.: clinical assistant (S.H.M.O.), children's psychiatric clinic, London Hospital.
IRONSIDE, DOROTHY N., M.B., D.P.H.: assistant M.O., Thanet area.

Manchester Regional Hospital Board:

BARRETT, E. L., M.B. Manc.: senior casualty officer, Stockport and Buxton hospital group.
BEDFORD, G. T., M.B. Edin., D.O.M.S.: consultant ophthalmologist, Barrow and Furness hospital group.
COCKETT, N. F., M.B. Lond., F.F.A. R.C.S., D.A.: consultant anæsthetist, Burnley and district hospital group.
GAGE, ALBERT, M.B. Aberd., D.P.M.: consultant child psychiatrist, local authority clinics at Wigan, Bolton, Rochdale, and Salford, with an attachment to Booth Hall Children's Hospital, Manchester.
GILMAN, P. W., M.B. Manc., M.R.C.P., D.M.R.D.: consultant radiologist, West Manchester hospital group.
KENYON, W. I., M.B. Glasg., M.R.C.P.: consultant physician, Ashton, Hyde and Glossop hospital group.
MEDCALF, MARY S., M.B. Birm.: senior casualty officer, Westmorland County Hospital, Kendal.
O'BRIEN, T. D., M.B. N.U.I.: assistant physician in geriatrics, Oldham and district hospital group.
PEEBLES BROWN, R. A., M.B. Glasg., M.B. Cantab., F.R.F.P.S., M.R.C.P.: consultant physician, South Cheshire hospital group.
THAKURDAS, H., M.B. Lahore: senior casualty officer, Stockport and Buxton hospital group.

The Hospital for Sick Children, Great Ormond Street, London:

BARRACLOUGH, GEOFFREY, B.M. Oxon.: registrar, department of morbid anatomy.
CAMPBELL, A. G. M., M.B. Glasg., M.R.C.P.E., D.C.H.: house-physician.
CRUMP, MARGARET, M.B. Lond., D.A.: resident junior anæsthetic registrar.
HUGHES-DAVIES, T. H., B.M. Oxon., M.R.C.P.: senior medical registrar.
LEVY, A. HARRISON, M.B. Brist., F.R.C.S.: senior surgical thoracic registrar.
ROYSTON, N. J. W., M.R.C.S., M.R.C.P.E., D.C.H.: resident assistant physician.
STEVENS, L. H., M.B. N.Z., M.R.A.C.P.: medical registrar.
MACMAHON, R. A., M.B. Sydney, F.R.C.S.E.: senior surgical registrar.
WYNNE, J. M., M.B. Cape Town, F.R.C.S.: house-surgeon.
ZINKIN, PAMELA M., M.B. Leeds, D.C.H.: house-physician.

Colonial Appointments:

AZZOPARDI, E., M.D. Malta, D.OBST.: M.O., Jamaica.
DENING-SMITHERMAN, PETER, M.B. Lond.: M.O., Bahamas.
JORDAN, PETER, M.D. Lond., D.T.M. & H.: director, East African Institute for Medical Research, East African High Commission.
MACKAY, J. F., M.B.: pre-registration house-officer, Bahamas.
MURPHY, G. D., M.B. Belf., T.D.D., D.T.C.D.: senior M.O., Fiji.
RIGBY, E. P., M.B. Lond., D.P.H., D.T.M. & H.: chief M.O., Kenya.